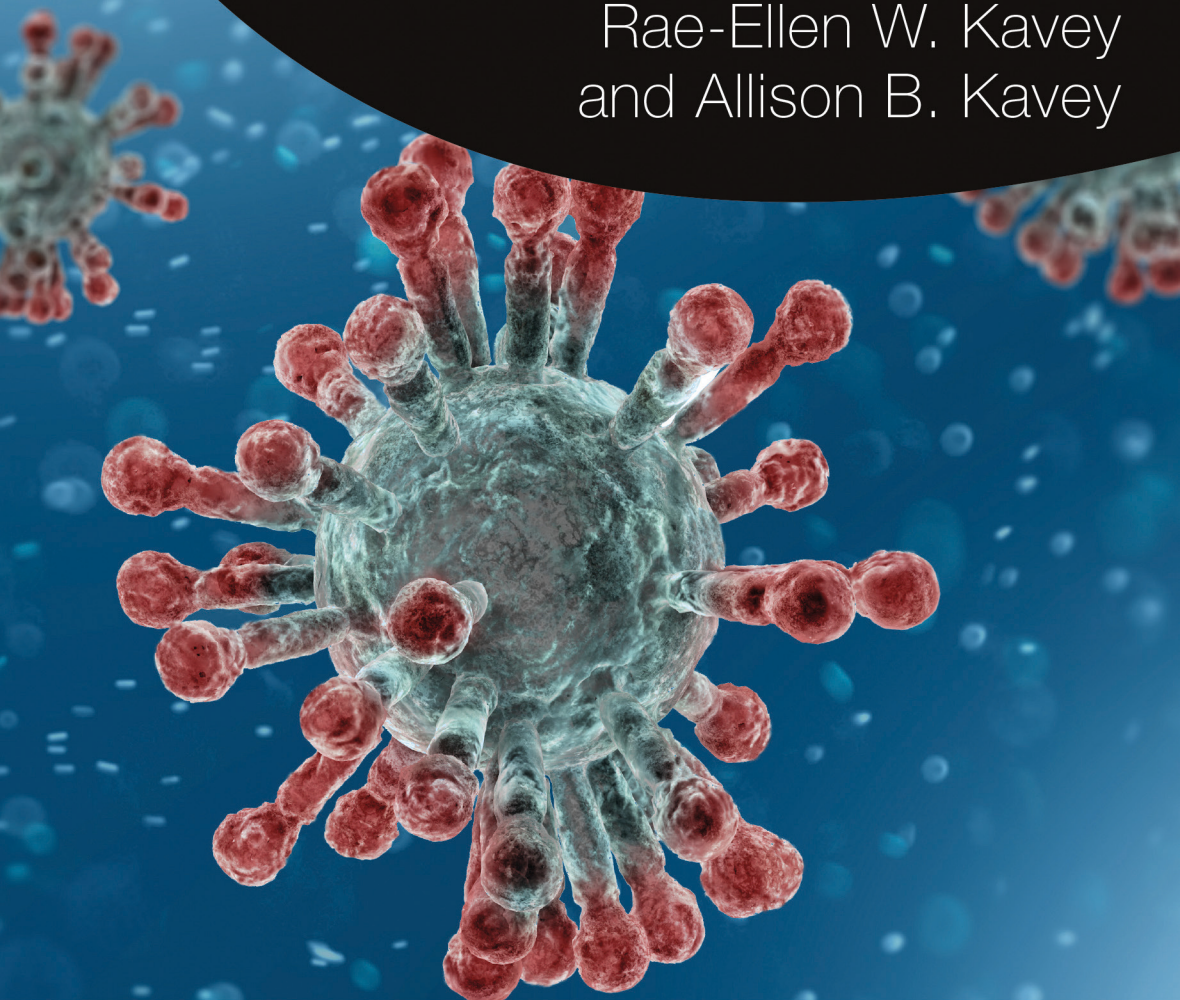


Viral Pandemics

From Smallpox to COVID-19

Rae-Ellen W. Kavey
and Allison B. Kavey



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VIRAL PANDEMICS

Written by a public health practitioner and a medical historian, *Viral Pandemics* explores the terrifying world of viruses as the cause of all acute pandemics since 1900, including the COVID-19 pandemic. The book illuminates the critical dual roles of viral biology and increasing global interconnectedness that have resulted in an escalating pandemic spiral.

Viral Pandemics is the first book to focus exclusively on pandemics caused by viruses and the first to report the COVID-19 pandemic. In each chapter, the historiographic narrative follows the path of the virus from its original detection through its first appearance as the cause of disease, to its emergence as an explosive pandemic. Scientific information is presented in an accessible, straightforward style in compelling narratives that introduce the extraordinary universe of diverse, opportunistic viruses whose remarkable capacities make them formidable adversaries. The book makes it clear that global viral disease challenges are a persistent reality with the potential to cause catastrophic loss of life and major social and economic damage. A summary chapter draws together lessons learned and develops a proposed multidisciplinary global response.

Viral Pandemics is the only book that provides a complete historical narrative focused on viral pandemics. This comprehensive survey is designed for students and scholars in biology, epidemiology, public health, global history and the history of medicine, as well as general readers interested in the science of pandemics.

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Dedications

REK

For Les, without whom there would be no book.

For Allison, who taught me what real history is.

For Molly, faithful companion who was with me through every page.

ABK

For my mum who found a way to bring two worlds of
knowledge together to make one book.

“Epidemics on the other side of the world are a threat to us all.
No epidemic is just local.”

Peter Piot

“Messieurs, c’est les *microbes* qui auront le dernier mot.”
(Gentlemen, it is the *microbes* who will have the last word.)

Louis Pasteur



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PREFACE

Of course, I knew about epidemics – or at least, I thought I did. After almost 35 years as a practicing physician with an additional master's degree in Public Health, epidemics were part of both my training and my experience. I had a longstanding interest in the history of medicine, including years of teaching medical students and undergraduates, where I had always presented epidemics as I saw them: major signposts in the evolution of science and medicine. Five years at the National Institutes of Health gave me a unique public health perspective on clinical medicine. In 2009, I had first-hand exposure to an epidemic response when I covered extra shifts in the Pediatric ED during the H1N1 flu epidemic. But as a pediatric cardiologist in academic medicine, epidemics were not a top-of-mind issue. The Ebola pandemic changed that completely, exposing me along with epidemiologists, virologists, medical historians and international healthcare providers all over the world to a disturbing new vision of contemporary viral pandemics.

It was the fall of 2014 – the Ebola epidemic ravaging West Africa was on every news cast when I realized how little I knew about this disease which was described by President Obama as a potential threat to global security. I thought I knew viruses – after all, they are the cause of the most common illnesses in children. But learning about viruses like Ebola introduced me to an extraordinary world of diverse, opportunistic pathogens whose remarkable capacities make them formidable adversaries. All the major epidemics since the turn of the last century have been caused by viruses. Each year, the World Health Organization develops a list of diseases to prioritize for research and development in public health emergency contexts. Any type of pathogen can be selected for prioritization, but the 2018 review identified seven known diseases, all caused by viruses, each considered to pose major public health risks and require intensive research efforts. It was appreciation of the danger inherent in the biologic diversity of emerging viral pathogens

and recognition of the enormous associated public health risk that first suggested viral pandemics as the focus of this book.

Historically, the study of epidemics has revealed recurrent themes that marked one disease outbreak after another – themes recognized with the plague, the first well-documented epidemic in history: introduction of a new contagion to a naïve population; the deficient state of general health and hygiene; and the lack of appropriate healthcare. These have been augmented by new, critical concerns: the ever-increasing world population density, rapid and frequent global travel, progressive urbanization, deforestation, increasing global poverty and increasingly substandard living conditions, recurrent global conflicts, and climate change. Many of these factors can be combined under the heading of increasing connectedness – population growth and frequent, rapid travel bringing people from all over the world closer and closer together, and once-isolated animals into increasingly intimate contact with humans. Since 1940, 60% of human infectious diseases have been caused by pathogens that originated in animals; disease experts predicted the next major outbreak would be caused by a virus that had jumped from an animal to infect humans – SARS-CoV-2 proves how right they were.

This book arose from two critical vantage points: mine, as an experienced physician with a public health background; and my daughter Allison's, as an academic historian of science and medicine. We've combined our experience as clinician and historian with extensive research to create a new approach to the evolving history of viral pandemics and its implications for a future global pandemic disaster. Beginning with smallpox and moving forward through yellow fever, polio, HIV/AIDS, West Nile virus and SARS, Zika and Ebola, plus the ongoing 2019–2020 SARS-CoV-2 pandemic, we present a comprehensive survey of epidemic viral disease from 1900 to the present. In each chapter, the narrative follows the path of the virus from its original detection through its first appearance as the cause of disease to its emergence as an explosive pandemic. We believe this allows readers to appreciate the unique biologic weapons of the virus, the dynamics of epidemic disease spread and the contemporaneous abilities of medicine and science to contend with the pathogen. In parallel, we identify the elements of connectedness that allowed a localized disease outbreak to become a global pandemic, giving readers the opportunity to appreciate the increasingly critical role that human encroachment plays in global disease. Each chapter begins with a brief personal narrative related to the subject of the chapter. These are intended to allow readers to relate directly to the content – to bring home the concept that no matter where we live, no matter how privileged our circumstances, we are all at risk for viral epidemic disease. At the end of each chapter, Allison provides a final historic perspective on a specific aspect of the pandemic. These focused analyses based on primary evidence sources provide scholarly insight on the ways in which the epidemic was understood by contemporaneous physicians, institutions and patients – and the ways current epidemics could be studied to optimize medical and scientific progress.

The book is an attempt to illuminate the critical path that viral pandemics have traced over the last century. And it is a warning that contemporary medicine

appears increasingly unprepared to deal with these epidemics, as terrifying viral agents emerge as highly infectious contagions at closer and closer intervals. It is only a matter of time until yet another virus emerges with the right combination of high infectivity, ready transmissibility and high mortality in a globally connected area. It is our hope that by critically exploring the biology of viral pandemics, the global context in which they occurred, and the corresponding response of science and medicine, we can elucidate the lessons of the past and potentially see how to best achieve a timely and effective response in the future.

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We thank our families for their love and support, especially Andy, for playing the “which virus is more awful?” game; Les, for unfailing love and for finding us an editor; Sarah, for always being willing to listen; Chris, for keeping REK totally informed on all things epidemic; and Rachel, for sympathy when it was really needed. And we thank our editor at Routledge, Grace McInnes, who took a chance on a first book by a mother and daughter team – your support has been invaluable.

1

A BRIEF INTRODUCTION TO VIROLOGY

Preventing the Unknown

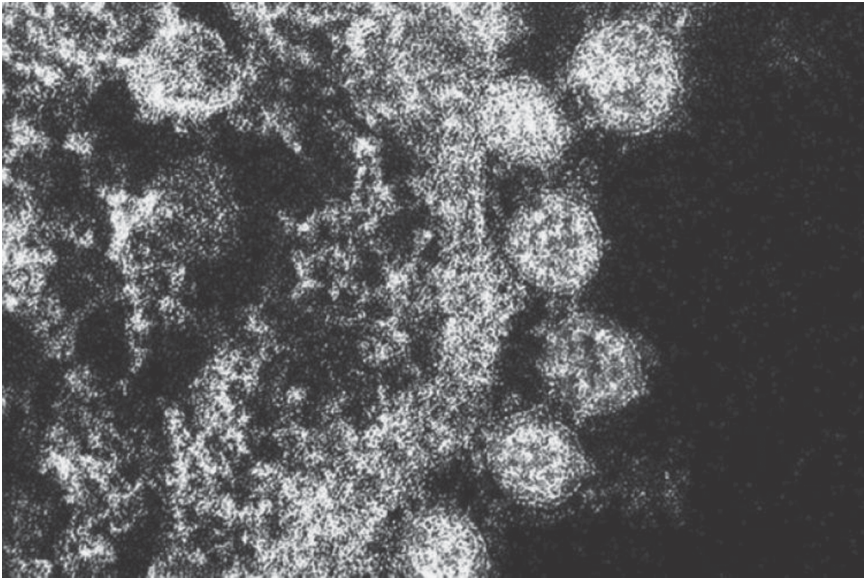


FIGURE 1.1 Transmission electron micrograph of coronavirus particles found near the periphery of an infected cell.

Source: Image captured at the US National Institute for Allergy and Infectious Disease (NIAID) Integrated Research Facility in Fort Detrick, Maryland. [NIAID.gov](https://www.niaid.nih.gov).

Global health in the twenty-first century faces unprecedented challenges from powerful, highly pathogenic viruses. These invisible but enormously powerful agents have already caused a series of terrifying disease outbreaks; since just the turn of the century, we have faced the continuing global spread of HIV/AIDS, SARS (Severe Acute Respiratory Syndrome), a global influenza pandemic with a newly emerged H1N1 strain, the global spread of Zika with its devastating pre-natal consequences, overwhelming and ongoing Ebola pandemics, and now a growing pandemic due to the newly recognized coronavirus shown in Figure 1.1. In each case, the unique abilities of the causative virus were critical elements in determining the outcome of the pandemic. To understand the intrinsic factors that determine viral pathogenicity, we begin by tracing the history of virus discovery.

The story begins in the sixteenth century with Girolamo Fracastoro, a Renaissance scholar of philosophy, poetry and medicine who studied with Copernicus at the University of Padua. At the tender age of 19, he was appointed as a professor at the University and elected the official physician of the ecumenical council of the Roman Catholic Church. From his earliest days, he adopted a scientific approach to the study of nature and this may have led to his absorption in understanding the causes of disease. In his 1546 work, *De Contagione et Contagiosis Morbis* (*On Contagion and Contagious Diseases*), he described his theory that infection results from “tiny, self-multiplying bodies that can be spread by direct or indirect contact, through infected objects, or even through the air over long distances.”¹ This idea of infectious “contagion” had been suggested by others since antiquity, but Fracastoro’s explanation was the first clear articulation of the concept. At the time, his views were completely ignored in favor of the erroneous “miasma theory”: that lethal disease-causing agents arose spontaneously from decomposing material in the earth that traveled by air as a poisonous, foul-smelling vapor. Given the ghastly stench that arose above communities in the Middle Ages without any form of sewage management, it is easy to understand how this theory persisted. It was the mid-1800s before the French microbiologist, Louis Pasteur, determined that it was microscopic bacteria that caused disease and Robert Koch defined the procedure for proving that specific diseases are caused by specific bacteria, essentially formalizing Fracastoro’s theory as the germ theory of disease.²

Bacteria are the smallest microbes which can survive independently because they carry all the necessary cellular machinery and genetic material to produce energy and reproduce within a single cell. Confirmation of bacteria as the cause of disease transformed the practice of medicine, and by early in the twentieth century, practical extension of the germ theory led to many improved public health sanitation practices like water treatment and sewage disposal. Public education increased awareness of the ways in which bacteria thrive and this supported improved personal hygiene practices like handwashing and safe food preparation. While antibiotics as specific treatments for bacterial infections did not appear until much later in the twentieth century, public health improvements reinforced by comprehension of the

germ theory of disease significantly decreased deaths from infectious diseases in the early 1900s.

Within this context of increasing scientific knowledge and improving public health, viruses were virtually unknown. Bacteria which could be recognized and identified with a light microscope were established as the “germs” of the germ theory. However, despite all the progress linking pathogenic bacteria with disease, a significant number of clearly infectious diseases remained for which no causative bacteria could be identified. It was the late nineteenth century before any progress was made with this dilemma. Scientists who were unable to identify a bacterial cause for a well-recognized disease of tobacco plants called tobacco mosaic disease (TMD) found that an extract of crushed leaves from infected plants passed through a filter that removed all bacteria still caused the disease: they theorized that the filtrate must contain a submicroscopic infectious agent.³ The filterable agent was found to multiply only in an environment that included tobacco leaf cells, not in a cell-free environment. This demonstration, confirmed subsequently for all these tiny submicroscopic agents, led ultimately to the conclusion that they were parasites, obligate intracellular organisms which could replicate only in a plant, animal or human host. The term *virus* comes from the Latin word for poison and during the eighteenth and nineteenth centuries, it was used to describe all forms of infectious agents. Over time, *virus* became the specific term for these submicroscopic infectious agents. When the 1918 influenza pandemic occurred, viruses were known only as a mysterious group of tiny microbes that were infectious, filterable and required living cells for replication, but their structure and function remained unknown.³

While not specifically identified, viruses had caused disease as long as there had been life on earth, and outbreaks of viral disease were recorded for centuries, ever since humans began living together in communities. Smallpox was first reported in approximately 10,000 BC and it is still considered to be among the most lethal viral infections. At around that same time, mumps, measles and polio, all caused by viral pathogens, were first described in ancient Egypt. While not necessarily identified as influenza, major flu outbreaks occurred throughout recorded history, beginning as early as 412 BC and extending right through the nineteenth century. The yellow fever virus – the first virus specifically recognized as causing human disease – was identified in 1900. In 1909, poliomyelitis was definitively shown to be caused by a virus. By the early twentieth century, viruses had a long and tragic record of causing serious pandemic disease.

It was at this time that the effort to understand viruses became inextricably linked with the devastating 1918 influenza pandemic (more to follow on this pandemic in Chapter 4). Faced with a terrifying disease outbreak for which they had no treatment, doctors and scientists struggled to find a comprehensible bacterial cause, a search which continued long after the pandemic ended. At that time, a viral etiology could only be identified indirectly, by using an ultrafiltrate from a diseased subject to induce disease in a susceptible plant or animal host, or by detecting the presence of antibodies against the disease in survivors of the illness in question.

Using these indirect methods, viruses had been confirmed as the cause of a number of important human and animal diseases including smallpox, yellow fever, rabies and measles. In 1919, a year after the primary 1918 pandemic ended, scientists from Japan and from France reported separately that a bacteria-free emulsion of mucous or blood from influenza patients produced classical flu symptoms of varying severity when given to monkeys and to human medical volunteers.^{4,5} These results strongly suggested that influenza was caused by a virus but scientists were unconvinced, perhaps because at the time, so little was known about the basic nature of viruses.

It was not until 10 years after the influenza epidemic that a young American scientist named Richard Shope began studying swine flu, an influenza-like illness that had sickened millions of pigs in the Midwest in the fall of 1918, just as the lethal stage of the influenza pandemic began, and had continued as a seasonal illness in pigs since that time. Shope found that a filtrate of mucous from a pig with swine flu would produce a similar flu-like illness in a healthy pig – conclusion: the cause of swine flu was a virus.⁶ By this time, Wilson Smith, Christopher Andrewes and Patrick Laidlaw, three young British researchers, had identified the ferret as a good model for influenza, because the animals developed a classic flu-like illness described by the researchers as “fever, sneezing, mucopurulent nasal discharge and sticky encrustation around the nose” within 48 hours after instillation of nasal washings from human volunteers with the flu (I cannot help but picture cages full of miserable, congested ferrets!). Nasal washings from these infected ferrets were then shown to transmit the disease to other ferrets. In addition, injection of serum from ferrets who had recovered from the flu blocked development of the clinical disease. In 1933, these scientists published their work in *The Lancet*, confirming for all that human influenza was caused by a virus.⁷ Shope and the British team then collaborated and showed that ferrets inoculated with swine flu filtrate developed an illness indistinguishable from the experimental flu caused by the human flu virus. Did humans give influenza to pigs? Was the swine flu virus actually the human flu virus? Using serum from survivors of the 1918 pandemic, the team showed incomplete blocking of swine flu virus infection, suggesting that the swine flu virus and the human influenza virus were closely related but not identical.⁸ As there was no virus from the 1918 pandemic available for investigation, this swine flu connection could not be further evaluated at the time.

The next important discovery – and this was very important – occurred with attempts to develop an effective influenza vaccine: recognition of the capacity of the influenza virus for spontaneous mutation. Originally, all influenza disease was thought to be caused by the single virus identified in 1933, so vaccines were developed to prevent infection with this specific virus. The concept of immunity was well-established by the early 1900s, based on the historic observation that for many diseases, a single episode conferred lifelong resistance to recurrent infection. With the dawn of bacteriology, antitoxins and vaccines against several important bacterial pathogens including smallpox, diphtheria, tetanus, anthrax, cholera, plague and typhoid had already been developed. In Britain, Smith and Fellowes developed an experimental influenza vaccine using the 1933 virus strain in a mouse lung

model with the virus inactivated by formaldehyde. Tests with the vaccine in ferrets showed that it prevented influenza symptoms with an associated increase in neutralizing antibody levels. On this basis, they conducted a small trial in 30 soldiers in 1936; there was no flu outbreak for clinical comparison that year, but the vaccine did increase antibody levels. The next year, they gave the vaccine to 500 military men with 500 unvaccinated men as controls. The trial was a complete disaster! There was a major flu outbreak but the vaccine proved completely useless, with no difference in influenza cases between the vaccinated and unvaccinated soldiers. The team looked at all the available evidence that could explain the failure of their vaccine. They had already recognized that flu viruses from different years and from other parts of the world evaluated in their laboratory differed.⁹ This evidence of antigenic variation between strains was also recognized by American researchers, Thomas Francis and T.P. Magill, in 1936 using cross-neutralization tests.¹⁰ Putting all this information together, Andrewes and his team concluded that the complete failure of their vaccine prepared with the 1933 virus to prevent infection with the 1937 virus strain indicated that significant variation in the virus must have occurred between flu seasons. Recognition of spontaneous mutation of the influenza virus was a critically important revelation that explained a significant part of the dangerous potential of viruses, but at the time, it was seen as a perplexing problem with no solution.

By this time, viruses were recognized as having many of the characteristics already identified for infectious disease pathogens in general. In particular, transmission and infection – the processes by which viruses spread to and infect new hosts – were found to follow the patterns already described for bacteria. Because viruses cannot replicate without using the machinery of a host cell, transmission and infection of new hosts are of primary importance. After contact, viral pathogens can enter our bodies through the mucous membranes of the mouth, eyes, nose, or genital tract; or, through breaks in the skin barrier. There are five main routes of pathogen transmission to these potential entry sites – aerosol/airborne, direct contact, fomite, oral and vector – and viruses use them all. Airborne transmission involves the spread of droplets from the nose, mouth or respiratory tract of an infected person via sneezing, coughing, or talking – this is the primary mode of transmission for all the viruses that cause the common cold. Transmission by direct contact requires that infected skin, mucous membranes or body fluids contact the mucous membranes or a break in the skin of the new host – sexually transmitted diseases are primarily spread this way. Fomite transmission occurs when items used by infected individuals transfer the virus from one individual to another – countertops, clothing and bedding are all potential surfaces for viral contamination and transmission. Fomite infection involves a secondary exposure route, such as direct contact, for the pathogen from the contaminated object to enter the new host. Oral infection involves ingestion of food or water contaminated by the virus, but it can also occur by fecal–oral transmission, from the hands of an infected individual with poor hygiene to the hands and then the mouth of a new host. Infected insects or animals – called vectors – can also transmit viral disease: the most common vector

for human viral disease is the mosquito. Finally, viruses can be vertically transmitted from mother to baby during pregnancy and in the peri-partum period, across the placenta or through direct contact during or immediately after birth and during breast-feeding. This is an important mode of transmission for viruses that are carried in the blood and other body fluids. Many viruses use multiple modes of transmission – another way they maximize their potential to infect.^{11,12}

At Long Last: Virus Visualization

Between the 1930s and the 1950s, progressive understanding of viruses was inextricably linked to progress in imaging, genetics and molecular biology. Invention of the electron microscope (EM) in 1931 gave scientists the first images of viruses, which were seen to be extremely small, roughly 100–300 times smaller than bacteria, ranging from 20 to 400 nanometers in diameter.¹³ In 1935, examination of the infamous tobacco mosaic virus revealed the very simple basic structure of all viruses: a protective protein shell or capsid around a nucleic-acid core of either DNA or RNA, the viral genome, as depicted in Figure 1.2.¹⁴ This work showed that viruses were actually particles, not cells, with the capsid composed of protein subunits called capsomeres; the arrangement of capsomeres around the viral genome determined the shape of the virion. In some viruses, an outer layer was seen to envelope the capsid.¹⁵ As the smallest and simplest of known infectious agents, viruses were famously described as “a piece of bad news wrapped up in protein”.¹⁶

As early as the mid-1930s, researchers began studying bacteriophage, a type of virus which only infects bacteria. Bacteriophage do not cause disease in humans and multiply rapidly in large numbers so they are ideal subjects for the study of viruses. Beginning with EM visualization, Max Delbruck and Salvador Luria, young researchers at the Marine Biological Laboratory in Woods Hole, described

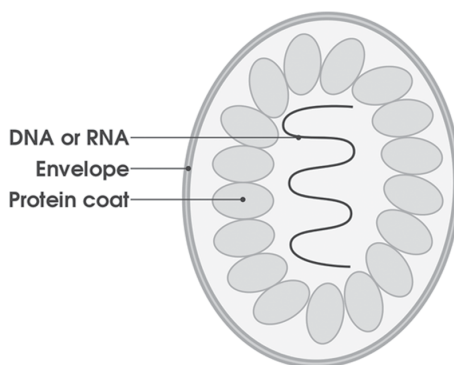


FIGURE 1.2 Basic diagram of a virus.

Source: domdomegg/CC BY (<https://creativecommons.org/licenses/by/4.0>).

the process of viral replication.¹⁷ Outside of a host cell, they showed that a virus was metabolically inert, but when contact was made, the virus inserted its genetic material and took over the cell's functions. Newly created virus components were assembled into thousands of new viruses – called virions – which left the host cell, either by bursting through the cell membrane and killing the host cell, or by budding through the cell membrane, in which case the cell survived and could function as a viral reservoir.¹⁸ In either case, the released virions then went on to infect new host cells. Over the next several decades, viruses were found to use cell-surface glycoproteins to recognize and bind to specific protein or carbohydrate receptors on a host cell's outer surface. This complex process is the mandatory, initiating step in cell infection and the identification of virus receptors and the characterization of virus–receptor interactions remains an important research target in virology.¹⁹

In 1945, the Delbrück–Luria team made another critically important discovery when they described genetic recombination: two virus particles simultaneously infecting the same cell could exchange parts of their strings of genes resulting in new, hybrid forms of the original viruses.²⁰ Along with Alfred Hershey, Delbrück and Luria received the 1969 Nobel Prize for medicine because of their “discoveries concerning the replication mechanism and the genetic structure of viruses”.²¹

Molecular Genetics

Viral studies were critical to the new and important field of molecular biology. Beginning in the mid-1940s, scientists focused on identifying the exact nature of the biomolecule that carries hereditary information. Although the five nucleotide bases – adenine, cytosine, guanine, thymine and uracil – had originally been described back in 1910, it was not until 1950 that Erwin Chargaff and his team discovered that within deoxyribonucleic acid or DNA, thymine (T) is always paired with adenine (A) and cytosine (C) is always paired with guanine (G).^{22,23} In 1952, working again with bacteriophage, Alfred Hershey and Martha Chase showed that DNA is the molecule that carries all the genetic instructions for cell growth and replication.²⁴ In 1953, Watson and Crick famously identified the double helix structure of DNA, based on work in viruses, and crystallographic and x-ray diffraction images obtained by Rosalind Franklin and Maurice Wilkins.²⁵ They showed that human cells contain two strands of DNA, each composed of sequences of the four nucleotide bases. The nucleotide bases in one strand are paired with their complementary partners in the opposite strand – A with T, C with G – to form the connecting rungs of the DNA ladder. Viruses use the same system of matching base pairs in their DNA, but they have a very simple genome, averaging only 3–400 genes, compared with 20,000–25,000 genes in the human genome.²⁶ In 1956, a series of experiments culminated in the demonstration that ribonucleic acid or RNA could also be the carrier of genetic information when this was shown to be the case for the infamous tobacco mosaic virus.²⁷ However, the adenine–thymine base pairing in DNA is replaced with adenine–uracil pairing in RNA. In

1984 – more than 60 years after the Great Influenza Pandemic – the influenza virus was found to be a single-stranded RNA virus with eight segments.²⁸

Understanding the structure of genetic material led to recognition that point mutations – spontaneous changes in a single nucleotide – were common to all cells, bacteria and viruses and this was identified as an explanation for ongoing variation, like that recognized with the influenza virus back in the 1930s. With point mutation, these small, subtle changes are incorporated into the viral genome, a process called *genetic drift*, which can result in literally thousands of viral lineages and sublineages. Mutation rates differ significantly between DNA and RNA viruses because the process of DNA division is highly regulated with specific checkpoints to detect miscopied DNA and eliminate major mutations. RNA viruses have no such system and therefore have much higher mutation rates, approximately one mutation per genome copy.²⁹ Only mutations that do not interfere with essential viral function survive, but the high mutation rate in RNA viruses leading to a veritable cloud of mutant descendants provides many opportunities for this to occur.

The process of recombination identified by the Cold Springs Harbor team – two virus particles simultaneously infecting the same cell exchanging parts of their genetic material to produce new hybrid forms of the original viruses – was found to occur primarily in DNA viruses and was recognized as resulting in new viral strains which could infect previously resistant hosts, an important part of the infectivity of viruses. A particular form of recombination called “reassortment” occurred only in RNA viruses with segmented RNA, like the influenza virus. In this setting, whole segments of genetic material are exchanged, resulting in progeny with immediate and major antigenic change, a process called *genetic shift*.³⁰ Based on findings like these, it was recognized that reassortment could yield an entirely new and antigenically novel virus strain. In the 30 minutes needed for a virus replication cycle, an infinitesimal killer virus could emerge, highly infectious, easily transmissible and lethal. It was molecular genetic work that identified this most important characteristic of RNA viruses: endless evolution by both spontaneous mutation and by genetic reassortment leading to continuous emergence of new, antigenically novel strains. Faced with an entirely new virus strain, human hosts have little if any resistance, so these emerging strains have high infectivity. This is especially true when reassortment occurs between an animal virus and a human virus.

In addition to the capacity for reassortment, some viruses have an unexpectedly wide host range with natural hosts that are infected in a primary transmission cycle and alternative hosts which can be infected by spillover from that original species to another. This species cross-over was recognized by Richard Swope when he found the human influenza virus from the 1918 pandemic had crossed over to infect pigs.⁶ An important part of the dangerous potential of viruses emerges when a virus is transmitted directly from animals to humans. Spillover of a virus across the species barrier to infect a human exposes an immunologically naïve subject to a potentially devastating new pathogen. Such zoonotic transmission requires intimate contact between animals and people so historically, it was identified in domestic animals.³¹ As increasing global population density has brought

wild animals and human populations into closer and more frequent contact, new infectious disease threats are often found to have wildlife origins. Zoonotic viruses are the most frequent newly emerging human pathogens, constituting 85% of all pathogens discovered since 1980.³² With their high rates of nucleotide substitution, poor mutation error-correction ability and therefore higher capacity to adapt to new hosts, RNA viruses have been identified as a major threat for cross-species infection. Reservoir infections are a final and important source of viral survival and infectious potential. Viruses cannot survive independently, but they can be sustained in animal or human hosts who have no apparent signs of disease but serve as an ongoing source of infection and of genetic material for the emergence of unique and dangerous new pathogens.³³

Identifying the Evolutionary History of Viruses

Development of techniques for gene sequencing led to phylogenetic evolutionary analysis, an important tool for describing the interconnected evolutionary histories of living organisms based on their molecular sequences. This is actually a derivation of the concept first described explicitly by Charles Darwin, who used morphological characteristics to determine the degree of similarity between organisms and thereby imply an evolutionary relationship.³⁴ As molecular techniques became available providing detailed, unambiguous identifiers in the form of DNA or RNA sequences, these replaced the old, indirect methods.³⁵ DNA or RNA sequence analyses provide explicit information about the entire genome of an organism. Comparison of sequencing data from different organisms allows construction of a tree-like pattern that depicts the evolutionary relationships among the group. Because of the number and complexity of nucleotide sequences in most comparisons, computer programs are used to perform the analyses. These techniques allow visualization of the origin of changes in disease severity and transmissibility of specific pathogens.

A secondary goal of phylogenetic analysis is to determine the *timing* of ancestral sequence divergence. In RNA viruses where spontaneous mutation (i.e., divergence) is common, phylogenetic analysis can determine when separate genetic lineages arose relative to each other. This concept gave rise to the idea of a *molecular clock* – using the mutation rate of biomolecules to determine the time in prehistory when two or more biomolecules diverged, with the benchmark time before divergence based on fossil or archeological dates.^{36,37} Timing the emergence of new mutations is important in analysis of viral epidemics because it allows us to infer the pattern and order of evolutionary change, especially when correlated with historic data.

The Infinite – and Infinitely Powerful – Virosphere

Early viral research focused on the identification of pathogenic viruses as the cause of specific diseases. Scientists developed a relatively simple system of viral classification based on the type of nucleic acid (DNA or RNA); the shape of the virus

capsid; the capsid diameter and/or the number of capsomeres; and the presence or absence of an envelope. Over time, we have recognized that disease etiology is an exceptionally narrow lens with which to view the vast world of viruses which are the most abundant entities on the planet. By focusing on viruses that cause disease, we have identified only a tiny fraction of the earth's virus population. Viruses are the most abundant life forms in the ocean with "10 billion viruses per liter of sea water."³⁸ They play a role in all the earth's ecosystems, but our understanding of this is still largely unexplored. Within the human microbiome – the ecological community of commensal, symbiotic, and pathogenic microorganisms that share our body space – there are literally millions of stable viral communities which scientists are only beginning to study via recent advances in sequencing and bio-informatic technologies.³⁹ And the number of virions in the virosphere – the universe of viruses on the planet – is almost beyond comprehension: a recent study in the Sierra Nevada mountains found 800 million viruses cascade onto every square meter of the earth's surface every day!⁴⁰

Viruses are formidable enemies. Despite their tiny size and minimal structure, their inertia and inability to independently replicate or produce energy, viruses have remarkable capabilities. Their extraordinary diversity, their remarkable capacity for rapid evolution and their ability to infect multiple species, allow them to endlessly evolve into novel forms that can cause new diseases, capable of sweeping through whole populations and leaving utter devastation behind. Multiple modes of transmission amplify the ability of viruses to cause infection. When a virus infects a living cell as shown in Figure 1.3, it can rapidly multiply and destroy its host; it can lie dormant, emerging to multiply or reassort at some later date; or it can co-exist within that reservoir host for generations. It is these multiple, unique capabilities which identify viruses as a major threat to human existence. In the following chapters, each dedicated to a specific viral epidemic, we will analyze the characteristics of the causative virus to identify the factors that allowed a local disease outbreak to explode into a global pandemic. In so doing, we will also explore a tiny fraction of the enormously diverse population of the earth's vast virosphere.

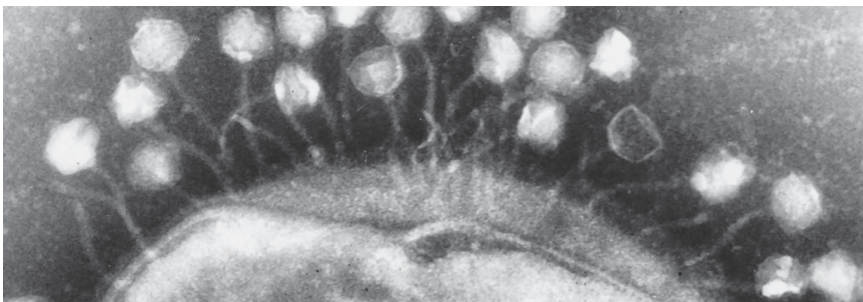


FIGURE 1.3 Viral bacteriophage attaching to a bacterium.

Source: Electron micrograph by Dr. Graham Beards. WikiMedia Fair use.

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2

THE SMALLPOX STORY

Gone but not Forgotten

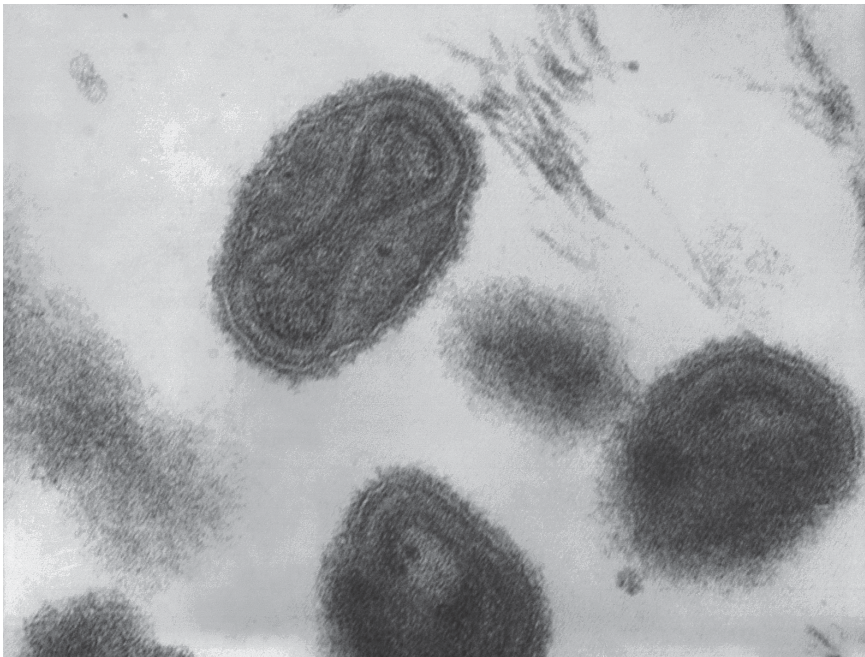


FIGURE 2.1 Electron micrograph of smallpox virus.

Source: Photograph courtesy of US Public Health Image Library. PHIL.CDC.gov

A SMALL REMINDER

Everybody remembers where they were when they first learned about the attacks on the World Trade Center. Like the assassination of JFK and the death of John Lennon, these events mark our hearts and our memories forever. But I'm guessing that many fewer will remember the other act of terrorism that occurred in that same month – a bioweapons attack that on this occasion took many fewer lives but had – and has – the potential to end the world as we know it.

On October 2, 2001, three weeks after 9/11, an infectious disease specialist recognized a possible case of inhalational anthrax in a critically ill man in Palm Beach County, Florida. On October 4, the diagnosis was confirmed when *Bacillus anthracis* was identified and Florida Department of Health and the Centers for Disease Control and Prevention (CDC) launched emergent epidemiologic and environmental investigations to determine the source of the patient's anthrax exposure. *Bacillus anthracis* spores were found at American Media Inc. in Boca Raton, where the patient worked as a photo editor. On October 5, this first victim of the anthrax attacks died, and subsequently it was determined that the spores that infected him had been contained in one of five letters with Trenton, New Jersey postmarks, mailed September 18, 2001, exactly one week after the World Trade Center attacks. The letters were mailed to ABC, CBS and NBC News and the *New York Post* newspaper, all in New York city, and the *National Inquirer* in Boca Raton, Florida – the site of the first victim's infection. Three weeks after the first mailing, two more letters containing anthrax with the same New Jersey postmark were mailed, addressed to two Democratic Senators, Tom Daschle and Patrick Leahy. At the time, Daschle was the Senate Majority leader and Leahy was head of the Senate Judiciary Committee. Ultimately, the letters infected 22 people with anthrax and five died.

The attacks on the World Trade Center were an unprecedented tragedy. But as a physician with a public health background, the 2001 anthrax attacks were an important personal wake-up call: at the time, I was only minimally aware of existing American biodefense efforts and the major thing I could recall about anthrax was that the bacteria causes pneumonia and creates spores which can survive for extremely long periods of time. I learned quickly: anthrax is a serious infectious disease caused by contact with the spores of the bacteria *Bacillus anthracis*. The most critical disease presentation is caused by inhalation of the spores, as occurred in the Florida case in this outbreak, associated with a mortality rate of more than 80%. Anthrax can be treated with antibiotics but its non-specific presentation often delays diagnosis until disease is far advanced. It is a well-known agent of bioterrorism.

It was sometime after 9/11, in those first weeks of fear and confusion and passionate patriotism, when the Department of Homeland Security was established and when American flags flew from every possible vantage point,

that I first heard the term “weapons of mass destruction,” or WMD, defined by the United Nations as a “nuclear, radiological, chemical or biologic weapon that can harm and/or kill a large number of humans or cause great damage to man-made structures, natural structures or the biosphere.” The first recorded use of the term is by the Archbishop of Canterbury in 1937 in reference to the aerial bombardment of Guernica, Spain:

Who can think at this present time without a sickening of the heart of the appalling slaughter, the suffering, the manifold misery brought by war to Spain and then China? Who can think without horror of what another wide-spread war would mean, waged as it would be with all the new weapons of mass destruction?

For most, I think WMD denotes nuclear weapons, but it is at least as likely that the next major terrorist attack will be chemical or biologic. Multiple sources make it clear that anthrax and smallpox were critical components of the American biological warfare program initiated by FDR in 1942, in response to reports that the Germans were preparing a biological weapon for use against the Allies. The new American bioweapons team was working with Canada and Britain to create biological cluster bombs when the United States dropped the atomic bomb on Hiroshima, effectively ending the war. But during the Cold War, the American biological warfare program expanded, focused on methods for dissemination of biological agents like smallpox and anthrax in multiple settings. By 1968, we had developed effective techniques for mass delivery of biologic WMD when, unexpectedly, President Nixon announced the unconditional end of all US offensive biological weapons programs in 1969. In 1972, the United States signed the Biological and Toxin Weapons Convention, along with the United Kingdom, the Soviet Union and more than a hundred other countries. The signers agreed that all offensive biological weapons research would end and all existing biological arsenals would be destroyed. Subsequently, the United States focused its bioweapons research on defense, but attacks with biologic agents and intelligence reports indicate that most other signatories neither stopped manufacturing new bioweapons nor destroyed their arsenals. According to Russian defectors, the Soviet bioweapons program actually accelerated after 1972 with both smallpox and anthrax as major components. Biologic WMD are a critical international concern.

The investigation of the 2001 anthrax attacks was a long, complex narrative of intrigue and ignorance. At the outset, the FBI focused on determining whether there was any connection with the World Trade Center attacks, eventually concluding that the anthrax attacks were an independent act of domestic bioterrorism. A critical early error was made in October of 2001, when the FBI and the CDC agreed to the destruction of a large collection of anthrax spores collected over more than seven decades and stored at Iowa State University,

eliminating the possibility of matching the strain of anthrax used in the attacks and a strain in the collection which might have allowed early identification of the perpetrator. As it happened, the FBI “Amerithrax” Task Force – which consisted of investigators from the FBI, the US Postal Inspection Service, and other law enforcement agencies, as well as federal prosecutors from the District of Columbia and the Justice Department’s Counterterrorism Section – expended thousands of investigator work hours on the case, which included collection of 5730 environmental samples from 60 locations. New genetic methods were even developed for analysis of anthrax to trace the origin of the anthrax spores. Ultimately, the attacks were attributed to an American government scientist with a history of mental illness who was a longtime anthrax researcher. He committed suicide in 2008, just as the FBI was preparing to charge him. The case was finally declared closed in 2012 but there are still doubts about the conclusion of the investigation. It is clear that in the anthrax letter attacks of 9/11, we escaped a potentially devastating epidemic because it is estimated that under ideal weather conditions, release of just one kilogram of anthrax spores over Washington DC could infect up to 50,000 people.

The anthrax attacks precipitated a complete overhaul and escalation of the American biodefense program which had been relatively untouched since 1972. New guidelines for preparedness against bioweapons were developed and disseminated by the CDC focused on diseases that can be directly transmitted between people and have high mortality rates, especially smallpox and anthrax. Despite its complete eradication in 1980, smallpox is still considered a first-line potential biologic weapon. Whether the many, diverse defense efforts that were initiated following 9/11 are in any way effective remains to be seen. But everything I read about biologic weapons of mass destruction raised the specter of smallpox as a key component in that armamentarium. And that led me to the two opposing stories in this chapter: the history of smallpox and its eradication as a clinical disease, and its ongoing role as a potential WMD ...

The Smallpox Story: Gone but not Forgotten

On May 8, 1980, the World Health Organization announced that after a 10-year campaign, smallpox had been eradicated from the face of the earth.¹ This has been hailed as the greatest public health achievement in medical history. It has certainly been effective in limiting contemporary medical experience with this dreaded disease: in almost 40 years of practice, my only exposure to smallpox was my own vaccination scar. So in a book focused on illuminating the progressive threat of emerging viral pandemics, where is the place for an eradicated disease like smallpox? The answers are clear: first, the campaign stands as a model for how application of epidemiologic and pathogen-specific knowledge plus sheer human persistence can alter the course of even the deadliest diseases; and study of how

smallpox eradication was accomplished provides important lessons for current and future disease eradication efforts. Second, the story of smallpox as a potential bio-terrorist weapon shows us that with powerful viral pathogens, we are never safe.

The Disease

Smallpox is a ghastly disease. Infection occurs through inhalation of the airborne *Variola major* virus depicted in Figure 2.1 via droplets from the nose or mouth of an actively infected individual, from face-to-face contact or by direct contact with contaminated objects such as bedding or clothing. The virus is very highly infectious – susceptible persons have up to a 90% chance of contracting the disease if they are exposed to someone who is infected. There is a 12–14-day incubation period before symptoms begin. Once inhaled, the virus invades the lining of the mouth and throat, migrates to regional lymph nodes in the neck and begins to multiply. During the incubation period, the infected individual is asymptomatic and non-infective. Around the 12th day, lysis of infected cells occurs and the virus explodes into the bloodstream in large quantities with further viral multiplication in the spleen, bone marrow and lymph nodes. Initial symptoms at this time are non-specific and include fever, myalgia, malaise, headache, nausea, vomiting and backache followed by the appearance of the first visible lesions, small reddish spots in the mouth and throat. These lesions rapidly enlarge and ulcerate, releasing large amounts of virus into the saliva, at which point the individual becomes very highly infectious. In 90% of patients, the characteristic skin rash begins 24–48 hours later, first on the face with rapid spread to proximal portions of extremities, the trunk, and lastly the distal extremities including the palms and soles. The ultimate distribution is worst on the face and extremities. The virus invades the lowest levels of the skin, the dermis, via the capillary blood supply. By the second day of the rash, the macules become raised papules and by the third or fourth day, these become vesicular, filled with an opalescent fluid which becomes turbid within 24–48 hours as the pustules fill with tissue debris. This stage lasts 24–36 hours, after which no new lesions appear. Over the next 5 days, the pustules enlarge so that in the most cases, the entire surface of the face is covered with sharply raised, tensely distended and extremely painful vesicles which are deeply embedded in the skin, literally tearing the dermis from its underlying support (Figure 2.2). In the typical case, fluid slowly leaks from the pustules over the next week, after which they progressively dry up and crust over. By the end of the third week of the illness, scabs have formed over all the lesions, which then flake off leaving depressed, depigmented, disfiguring scars. As terrible as smallpox looked, the suffering it caused was even worse as the pox lesions were intensely painful, making eating very difficult, every movement agony and sleep impossible.² The image in Figure 2.2 from the archives of the US Centers for Disease Control and Prevention (CDC) shows an unidentified child with the classic rash of smallpox.

The virus can be transmitted throughout the course of clinical illness, but this is most intense during the first week of the rash, when mouth lesions have ulcerated



FIGURE 2.2 Unidentified child with classic smallpox rash.

Source: CDC.

but most skin lesions are intact. Infectivity decreases as scabs form over the lesions, but the infected person is contagious until the last smallpox scab falls off. If stored in cool, dry, and dark conditions, the variola virus can survive in lesion crusts or tissues for months or even years.³ Infection from fomites – non-living objects or substances carrying infectious organisms and therefore capable of transferring them from one individual to another – was recognized during epidemics in the 1500s and this led to the practice of burning all the bedding and personal items associated with a smallpox patient.

With classic smallpox, death occurred in ~30% of patients due to a massive immune response that caused severe disruption of the clotting system with development of disseminated intravascular coagulation (diffuse clotting throughout the body, a common endpoint of severe systemic infection) and multiple organ failure. In the eighteenth century in Europe, 400,000 people died annually of smallpox, and one third of the survivors were blind.⁴ The case-fatality rate varied from 20% to 60% and left most survivors with disfiguring scars. The case-fatality rate in infants was even higher, approaching 80% in London and 98% in Berlin during the late 1800s.^{4,5} No wonder smallpox was viewed as “the most terrible of all the ministers of death.”⁴

Historically, there were some variations in the clinical presentation. Sometimes, the pustules merged into sheets, forming a confluent rash, which could begin to detach the outer layers of skin from the underlying flesh – a ghastly, incredibly painful variation. Patients with confluent smallpox often remained ill even after scabs formed over all the lesions. In 5–10% of cases, a malignant form of the disease developed where the skin lesions remained almost flush with the skin. Historically, this was much more common in children and was associated with prolonged high

fever, extensive rash of the mouth and throat and severe symptoms of systemic illness. Skin lesions matured slowly and by the seventh or eighth day were still flat and appeared to be buried in the skin. Finally, in ~2% of adult cases, a hemorrhagic form of the disease developed with subconjunctival bleeding in the eyes and internal hemorrhage in the spleen, kidney, muscle, and other organs accompanied by derangements of the clotting system. Death often occurred suddenly between the fifth and seventh days of illness, when only a few insignificant skin lesions were present. With each of these variations, the fatality rate was higher than with classic smallpox, ranging from 60% to 90%.²

Late in the nineteenth century, a milder form of smallpox appeared, originally in South Africa, South America, Europe, and Australia and subsequently in the United States. This much less serious disease was called *Variola minor* or *Variola alastrim* in contrast to *Variola major*, the classic form of the disease. Although individuals infected with *Variola minor* did develop characteristic pox lesions, the pox were widely separated and victims generally felt well throughout the illness, with no disfiguring scars after recovery and no risk of blindness. The mortality rate was only 1%. But importantly, surviving either *Variola major* or *Variola minor* provided lifelong immunity to both forms of smallpox.²

From the earliest descriptions, the marks of smallpox determined how it was defined. The word “variola” was applied to smallpox beginning in 570 BCE, as a term derived from the Latin “varius” which means stained, or “varus” which means mark on the skin.⁴ Smallpox was the full name given to the disease to differentiate it from syphilis (the “great pox”) and other diseases with rashes that also left residual scars. The date of first appearance of smallpox is unclear. Historical records suggest it evolved from a virus affecting animals – most likely rodents – and made the leap to humans in about 10,000 BCE, when the river valleys of Egypt and the Middle East were first settled. The smallpox virus only survives within the body of humans, so from that point onwards, it passed in a chain of infection from the ancient world right into the modern age. Historically, what are considered to be signs of smallpox infection have been found on skeletal remains from Africa as early as 10,000 BCE.⁶ Mummies recovered from 1570 to 1085 BCE in ancient Egypt are thought to demonstrate smallpox scars, most famously, the mummy of Ramses V.^{4,5} In 430 BC, a major epidemic is thought to have occurred in Athens, Greece, chronicled by Thucydides. This was the first time it was recorded that those who survived smallpox were subsequently immune, an observation confirmed by Abu Bakr Mohammad Ibn Zakariya al-Razi, known in the West as Rhazes, the leading scholar of the early Islamic world.⁷ Traders are thought to have carried the disease from the Mediterranean to India during the first millennium BC.^{6,8} Smallpox may even have contributed to the decline of the Roman empire, when in 108 AD, it is thought to have been the cause of an acute illness in the city of Antonine which killed as many as 7 million people.^{4,9} However, this early history is unconfirmed, because smallpox is never described in the Bible and is absent from the literature of the Greeks and Romans, with no description in the works of Hippocrates.¹⁰ From

India, smallpox spread into China in the first century AD and reached Japan in the sixth century.

It is clear that smallpox appeared in Europe during the Middle Ages, apparently coming from both Asia and Africa following trade and migration routes and the paths of the crusaders. We know that “pox houses” were built in the era of the Crusades, along the routes from Europe to the Holy Land. Some historians believe smallpox in the medieval period was a much less severe form of the disease and that over time, smallpox grew more and more deadly. By the sixteenth century it was endemic throughout Europe with cyclical epidemics causing severe mortality. Smallpox continued to ravage Europe, Asia, and Africa from the 1600s into the 1900s. By the eighteenth century, smallpox in Britain was at its height. It was at this time that the great Victorian historian Lord Macaulay wrote:

The smallpox was always present, filling the churchyards with corpses, tormenting with constant fear all who it had not yet stricken, leaving on those whose lives it spared the hideous traces of its power, turning the babe into a changeling at which the mother shuddered, and making the eyes and cheeks of the betrothed maiden the objects of horror to the lover.⁴

In the last half of the 1700s, smallpox accounted for 10–20% of all deaths in England and Scotland. It was famously described as a disease of “princes and paupers,” and the royal dynasties of Europe were particularly badly hit. In the first eight decades of the eighteenth century, smallpox killed an Austrian emperor, a king of Spain, a tsar of Russia, a queen of Sweden, and a king of France. Smallpox also had a devastating effect on England’s ruling elite: Charles II’s brother and sister were both killed by smallpox; his nephew, King William III, suffered smallpox; and William’s wife, Queen Mary, died of it. William’s successor Queen Anne caught smallpox and survived, but her son, Prince William, the heir to the throne, died – and this ended the Stuart line.⁴ The worldwide death toll was staggering well into the twentieth century, with total global mortality estimated at 300–500 million, vastly exceeding the combined total of all deaths in all world wars.

Spanish and Portuguese explorers introduced smallpox to the New World, where it devastated the native populations of the Americas who, having never encountered it before, had no immunity to it. The fate of the New World and the Caribbean was in many ways determined by this disease, which ravaged indigenous populations from the fifteenth century onwards into the twentieth century.^{11–13} Half the native population of Puerto Rico died of smallpox within a few months in 1519. When Spanish explorers encountered the Aztec civilization of Mexico, they carried the smallpox virus with them: within a few months, half the Aztec population had died, allowing a few hundred Spanish conquistadors to conquer this ancient civilization.

In North America, too, smallpox eliminated native tribes: in the three years before the *Mayflower* landed on the coast of New England, 90% of the native population of Massachusetts reportedly died of the disease. This tragedy continued well into the nineteenth century: as American pioneers expanded westwards across

the continent, they brought smallpox epidemics to decimate naïve, aboriginal populations wherever they were encountered. In the United States, more than 100,000 cases of smallpox were recorded as late as 1921.¹⁴

With such a dreaded and ubiquitous disease, it is perhaps not surprising that historically, doctors and scientists turned their efforts toward prevention. From the time of the Athenian plague in 430 BC, it had been recognized that smallpox survivors were immune to further infection. Based on this observation, multiple techniques developed to allow deliberate exposure to tiny doses of smallpox in the hope that immunity would occur without severe illness.¹⁵ An early effort in China involved blowing powdered smallpox scabs through a tube into the nostrils of a healthy person.¹⁶ Most popular and most effective was the variolation technique of inoculation: infected matter was taken from a pox of an infected person and spread into a fresh cut made on the skin of someone who had never had the disease. In the best-case scenario, the inoculated person developed a very mild case of the disease, was left unscarred and able to see, and could never be infected again. This process was developed in Africa, India, and China sometime before the tenth century, and was introduced to the Ottoman Empire by Circassian traders around 1670.^{17,18} They had good reason to do so – they sold slave girls into sultan's harems, and rather than having their merchandise scarred by smallpox and thereby rendered valueless, they inoculated them before sending them to court. These women introduced the practice into the Ottoman Empire, where Europeans first encountered it.

The variolation technique was described by an English ambassador to Turkey in 1714 in a letter home, and it became an accepted part of English aristocratic culture due to the efforts of Lady Mary Wortley Montague.¹⁹ Lady Montague was an aristocratic beauty who was infected with smallpox in 1715 and left horribly scarred; she lost her 20-year-old brother to the virus in 1717. Despite her scars, she married the diplomat Edward Montague, who was posted to Istanbul as ambassador to the central government of the Ottoman Empire. There, she learned about inoculation and began writing about its amazing efficacy to her friends in London. By inoculating her own children (her 5-year-old son in Istanbul and her 4-year-old daughter upon their return to London) in front of members of the royal court and urging her social circle to do so as well, she led the first public health inoculation effort in England.²⁰ That effort was picked up by the king, who commissioned a study by Charles Maitland, the physician who inoculated Lady Montague's children. Prisoners from Newgate Prison (in which residence had a higher mortality rate than smallpox!) were chosen to be inoculated. In exchange for their participation, they were pardoned. This trial proved successful – the prisoners survived and later proved immune to exposure to smallpox. Maitland moved on to orphanages for his next trial, and when those children also survived and were smallpox-resistant, he was called upon to inoculate the two daughters of the Princess of Wales. Their survival and subsequent immunity resulted in widespread acceptance across England, and variolation became standard practice for institutionalized children and adults, and for those

who could afford it.²¹ Performed correctly – with a tiny dose of smallpox material, administered just under the skin – variolation was very effective, and the most skillful variolators in the eighteenth century achieved impressive results in the fight against smallpox.

There were two significant problems with variolation: first, by introducing smallpox matter into the body, there was always the risk that the patient would contract a full-blown case of the disease. And indeed, approximately two out of every hundred patients variolated against smallpox in the eighteenth century died: this was significant, but a far lower mortality rate than among those who were naturally infected.² The second problem was that, after the procedure, the patient was transiently contagious, and could spread smallpox to others. Nonetheless, variolation spread across Europe through the mid-1700s, based on the success in England, the support of the Royal Society of Physicians and the English royal family.²²

In 1721, inoculation reached America, and with the support of Cotton Mather, a Protestant minister and Harvard-trained physician, and his colleague Zabdiel Boylston, it became broadly accepted in New England after a significant epidemic hit the colony there.²³ Religion was a powerful force in the world at that time and Cotton Mather's enthusiasm for inoculation was especially interesting because he couched it in religious terms. (For more on this, see the Historic Perspective at the end of this chapter.) Religious questions aside, the practice of inoculation spread throughout the American colonies, supported by Benjamin Franklin, who wrote in his autobiography:

In 1736 I lost one of my sons, a fine boy of four years old, by the small-pox, taken in the common way. I long regretted bitterly, and still regret that I had not given it to him by inoculation. This I mention for the sake of parents who omit that operation, on the supposition that they should never forgive themselves if a child died under it; my example showing that the regret may be the same either way, and that, therefore, the safer should be chosen.²⁴

George Washington had all his soldiers inoculated by variolation during the Civil War and attributed at least some of his ultimate success to the absence of smallpox among the troops.²⁵

Edward Jenner and the Development of Smallpox Vaccine

In the late 1700s in England, it was common knowledge that milkmaids who had developed cowpox were immune to smallpox and there were scattered reports of effective vaccination with cowpox material in England. Edward Jenner, a young British physician and scientist, took up this concept scientifically and used extracted fluid from a cowpox lesion to inoculate a young child. In a completely uncontrolled study, when the boy was injected with smallpox material 6 weeks later, there was no reaction. Although Jenner's original report of this case was rejected for publication by the Royal Society of Physicians, he persisted, adding new material, and

eventually he self-published this work. The report describes 10 cases of “vaccination,” his new term for the process to prevent smallpox, the word derived from *vacca*, Latin for cow.²⁶ Of note, Jenner also described inoculation with horsepox to prevent smallpox infection, a process called equination. Recent genetic analyses of extant vaccinia viruses have revealed horsepox virus genes in some strains, supporting the validity of this history.²⁷

Jenner’s paper received mixed reviews and vaccination did not immediately take off, but within a few months, many of his physician friends began asking for the vaccine. Vaccination spread as physicians adopted it and convinced their patients to try it instead of inoculation. They championed the procedure because vaccination was far safer: side effects were rare and there was no risk of developing smallpox disease. Jenner’s findings were confirmed by William Woodville, from the Smallpox and Inoculation Hospital in London, and by 1800, vaccination had reached most European countries and been adopted in the New World: Jenner was well on his way to becoming an international scientific superstar. In 1802, his place in history was guaranteed when the English Parliament granted him a patent on the smallpox vaccine. Because he was not part of the inner circle of the Royal College of Physicians, he still faced scorn and ridicule from some in the English medical community, but by 1810, vaccination had won the day. Jenner was the first person to make a scientifically based attempt to control an infectious disease. He established the practice of vaccination and understood the important implications of his work. As early as 1801, he wrote of vaccination “the annihilation of the smallpox, the most dreadful scourge of the human species, must be the final result of this practice.”²⁸ In Jenner’s honor, Louis Pasteur changed the definition of the term “vaccine” to refer to any inoculated material that produces disease immunity.²⁹

Originally, the pox material used for vaccination was kept alive by being transferred from arm to arm, including serial infection of children as a way to transport the virus across the ocean from Europe to the Spanish colonies in the Americas early in the nineteenth century.³⁰ Contamination as a result of this arm-to-arm procedure led to inadvertent transmission of other serious diseases, including syphilis and tuberculosis, so the vaccine was subsequently produced on the skin of animals, primarily calves but also rabbits and horses.³¹ Somewhere in this process, the original cowpox vaccine agent was replaced by a brand new, previously unknown virus, which was called “vaccinia.” *Vaccinia* was subsequently found to be an immunologically distinct strain, thought to possibly be derived from the cowpox virus by repeated serial passage in animals.³⁰ Alternatively, *Vaccinia*, cowpox virus, and *Variola* are thought to all be derivatives of a common ancestral virus with cross-immunity insuring that infection with one provides protection against all. Whatever the origin, *Vaccinia* became the consistent agent used in vaccines against smallpox from the early 1900s.^{31, 32}

The vaccination technique evolved from multiple scratches of the skin with diffuse application of cowpox fluid to a standardized procedure using a bifurcated needle holding a droplet of manufactured vaccine. With either technique, a red

papule appears at the site after about 3 days, and by 7 days, this has the classical appearance of a mature pox lesion – an umbilicated vesicle containing turbid fluid surrounded by an inflamed halo that may continue to expand over the next 3 days. Swollen lymph nodes and fever are common but resolve as the pustule dries up and crusts over. The scab falls off within ~3 weeks leaving a small round scar, the mark of successful smallpox vaccination, which conveys full immunity to smallpox in more than 95% of persons for at least 5–10 years. Successful revaccination provides protection for more than 20 additional years.²

Historically, a range of remedies were used to “treat” smallpox, with no effect. Once vaccination against smallpox was established and available, vaccination within 3 days of exposure was shown to prevent or significantly lessen the severity of smallpox symptoms in the vast majority of people. Even if performed later – 4–7 days after exposure – vaccination modified the severity of disease. Other than vaccination, treatment of smallpox was primarily supportive, including wound care, prevention of super-infection, and fluid therapy. People with semi-confluent and confluent types of smallpox had therapeutic issues similar to patients with extensive skin burns and required intensive fluid management– this would still be a primary focus of treatment in this setting today. Flat and hemorrhagic types of smallpox would be treated with the same therapies used to treat shock, including fluid resuscitation, inotropes to maintain blood pressure and respiratory support.³³

Smallpox represents the first disease that primarily challenged the medical community to develop a strategy for preventing its spread rather than treating its symptoms. With the help of inoculation and then vaccination, smallpox came to be a much less common part of life across the globe. It would take another century before religious ideology and cultural practice would overcome the many lingering anxieties about whether it was acceptable to God to prevent a natural disease or how to weigh the relative risks of deliberately infecting someone with a potentially deadly infectious agent.

The Virus

How the smallpox agent was identified as a virus is somewhat confusing because much of the early research thought to be about *Variola major* actually involved *Vaccinia*, the cowpox-derived/mutated agent used in vaccination, rather than the smallpox virus itself. The assumption appears to have been that because the *Vaccinia*-based vaccine caused immunity to develop, *Vaccinia* must be very similar to *Variola*, the agent that caused smallpox – and smallpox was obviously much more dangerous to the investigator. Even before the first definition of viruses as filterable infectious agents not retained by standard bacteriologic filters and not visible by light microscopy, *Vaccinia* had actually been visualized by light microscopy as “inclusion bodies” in vaccine material, as had *Variola* in human cells and lymph of individuals infected with smallpox.³⁴ In 1906, Paschen introduced the idea that these “inclusions” seen by light microscopy were in fact infective smallpox virions.³⁵ At the time, potential visualization of the organism by light microscopy did not advance the theory that

Vaccinia and *Variola* were viruses because failure to be seen with standard techniques was one way that viruses had originally been recognized. Viruses could only be further identified indirectly, by inducing disease in a susceptible host with a bacteria-free filtrate from a diseased subject, or by proven prevention of re-infection in survivors of the illness in question.

Then, Adelchi Negri, an Italian microbiologist, showed that the infectivity of vaccine lymph persisted after the lymph had been passed through a filter that held back bacteria: this was the first strong evidence that *Vaccinia* – and by inference, therefore, the smallpox agent, *Variola* – was a virus.³⁶ It was not until 1932 that Ledingham showed that antisera against *Vaccinia* specifically neutralized infectivity, a second step in the identification of *Vaccinia* – and therefore the smallpox agent, *Variola* – as viruses.³⁷ Deliberately infecting a person with smallpox to induce disease would have been dangerous and unethical, but when injection of the *Variola* agent onto the chorio-allantoic membrane of a developing chick embryo resulted in characteristic pox, *Variola major* – the cause of smallpox – was at last confirmed to be a virus.³⁸

Variola has been classified as a member of the Orthopox group. Four orthopox viruses cause infection in humans: *Variola* (*major* and *minor*), *Vaccinia*, cowpox, and monkeypox. The *Variola* virus infects only humans in nature, although primates and other animals have been infected in a laboratory setting. *Vaccinia*, cowpox, and monkeypox viruses can infect both humans and other animals. *Variola minor*, *Variola major* and *Vaccinia* share common amino acid sequences: this explains the immunity to all three diseases that develops after infection with any one of them and the effectiveness of a vaccine based on *Vaccinia* in preventing development of *Variola*.³⁹

With the advent of electron microscopy and molecular genetics, *Variola* was seen to be a very large, brick-shaped virus.⁴⁰ In 1940, the viral genome was demonstrated to contain DNA, and subsequently, this was shown to be a single linear, double-stranded DNA genome of 186 kilobase pairs with a hairpin loop at each end connecting the two DNA strands.³⁹ The DNA is bound to proteins in a nucleoprotein complex called the core, shaped like a dumbbell in the center of the virus, surrounded by a lipid and protein membrane (see Figure 2.1). The pox virion is the largest of all virions and its genetic material is among the largest of all viral genomes. The highly accurate poxviral DNA polymerase has conserved the sequences of these genes among all orthopoxviruses. Genes in the central region encode proteins involved in replication and virion structure while the flanking areas contain genes encoding proteins that modify the intra- and extracellular environment to favor viral replication and spread.⁴²

Poxviruses differ from most other DNA viruses in that they replicate in the cytoplasm rather than in the nucleus of susceptible cells. To accomplish this, they have a battery of enzymes including DNA-dependent RNA polymerase which are used to transform basic building materials – amino acids, nucleotides and lipids parasitized from the infected cell – into components of the new virion. The DNA-dependent RNA polymerase transcribes messenger RNA into DNA. The virus also has an inner and outer membrane envelope; the outer envelope

contains viral-specific polypeptides, including hemagglutinin, which are involved in virus attachment to host cell surface membranes. Finally, the extreme virulence of the variola virus is derived from a set of genes that reduce the multiple defense mechanisms of host organisms. A complement-regulatory protein inactivates the host complement system and prevents the host cell from engaging the immune complement cascade. The virus can also use fusion proteins to expose the host cell to extracellular material, thereby promoting degradation.^{43,44}

Nucleotide sequencing of variola fragments began in the 1980s and ultimately, complete genome sequencing of variola strains collected between 1944 and 1977 was accomplished. Historic strains that affected European and American populations between the thirteenth and eighteenth centuries were all eradicated following the initiation of widespread vaccination. Comparative genomic analysis of 45 epidemiologically varied variola virus isolates from the last 30 years indicates low sequence diversity, suggesting little if any spontaneous mutation and, therefore, no difference in functional genes. Analysis of viral linear DNA suggests that variola evolution involved direct descent and DNA end-region recombination events.^{41, 42}

Phylogenetic analysis – nucleotide and/or amino acid sequencing of individual virus strains – allows measurement of molecular divergence between strains and can be used to construct a theoretical evolutionary tree. With smallpox, this kind of analysis has been limited because the only available viral strains have come from twentieth-century specimens obtained before eradication of the disease in 1980. Analysis of the *Variola* isolates from the WHO Collaborating Center Repository collected between the mid-1940s and the 1970s show very high nucleotide sequence similarity to two pox viruses that infect animals, the taterapox virus from West Africa and the camel pox virus from central Asia, supporting the idea that the human virus arose from an animal strain. There was minimal diversity between the *Variola* virus isolates, indicating a very low spontaneous mutation rate, with the greatest variation related to site of geographic origin.^{45,46} Evolutionary clock analyses can predict the time to the most recent common ancestor and for *Variola*, the branches have shown widely divergent results, ranging from 1374 years ago up to 50,000 years ago; this difference indicates either a recent or an ancient origin and reflects the incomplete molecular genetic evidence at the time.

Then in 2016, excavation of the crypt of a seventeenth-century Lithuanian church recovered the mummified body of a child. Radiocarbon dating yielded an estimated date of death between 1643 and 1665 AD. Analysis of genetic material allowed development of a complete *Variola* genome.⁴⁷ The lineage was found to have the same pattern of gene degradation as twentieth-century *Variola* strains, but the gene sequence recovered from the mummified body was shown to be the predecessor of all the known *Variola* genomes. This important finding strongly suggests that genetic diversification of the smallpox virus is a relatively recent phenomenon with the major known viral lineages appearing between the seventeenth and nineteenth centuries. The researchers concluded that the smallpox lineages which

caused disease in the twentieth century had only been in existence for approximately 200 years. These findings do not preclude an ancient history for smallpox, as earlier viral lineages could have disappeared because of natural selection, host resistance to older variants or random chance.⁴⁸ They do mean, however, that the exact origin of the smallpox virus remains a mystery.

Edward Jenner could hardly have made a more fortuitous choice for effective vaccine development and ultimately for disease eradication than the highly stable DNA virus, *Variola*. Humans are the only hosts and the only victims – there is no other disease reservoir; and there is no subclinical disease – every infected person displays the characteristic rash and therefore every case can be identified. With established, sustained immunity after vaccination with a widely available, safe and effective vaccine, the stage was set for disease eradication.

Smallpox Eradication

Despite an effective vaccine, smallpox remained a serious worldwide problem well into the twentieth century. Recurrent smallpox epidemics were usually followed by short-term intensive vaccination efforts, but these were complicated by minimal public health infrastructure in many parts of the world and by problems with vaccine quality, preservation and delivery. During World War I, there were massive smallpox epidemics in Russia, Germany and Austria with ~250,000 deaths per year across Europe. In the United States and Canada, the last major smallpox epidemics occurred in the early 1920s. In the United States, rates of smallpox infection decreased steadily as mandatory vaccination of schoolchildren was put in place throughout the first half of the twentieth century and the invention of the ice box made vaccine storage efficient. There has been no endemic smallpox disease in the USA since 1926.

While the United States and European countries were getting smallpox under control, the developing world still suffered from it. Infection rates were high in Africa, South America, and Asia, where vaccination was not as widespread as in the West. During World War II, cases of smallpox infection increased. Previously unexposed regions were overtaken by variola carried by foreigners, or by soldiers who brought the virus home from foreign lands. From 1941 to 1946, the percentage of countries in which smallpox was endemic rose from 69% to 87%. During that period, smallpox killed three to four million people annually.

In 1947, there was an outbreak of smallpox in NYC when a man who had recently visited Mexico became ill, was hospitalized, and died; after his death, he was found to have had smallpox.⁴⁹ A second case and then a third appeared and concern about epidemic spread surged. When the first case was recognized, the NYC Health Commissioner encouraged all New Yorkers who had not been vaccinated since childhood to be re-vaccinated. Free vaccine clinics were established throughout the city and vaccine was provided to private physicians for administration. After the second death, the mayor urged all 7.8 million New York residents to receive the vaccine. In support, police, fire, departments and hospitals were mobilized to

provide space for the effort. Two days later, epidemiologic investigation indicated that all three patients with diagnosed cases were related, indicating that, in all likelihood, the outbreak had been successfully halted through vaccination of known contacts. Despite this evidence that the outbreak had been contained, the city pushed forward with its “Be sure, be safe, get vaccinated!” program. Ultimately, 5–6 million people were vaccinated over a two-month period. This was the largest mass vaccination effort ever conducted for smallpox to that time and marked the last cases of smallpox in America.⁴⁹

Globally, smallpox outbreaks decreased through the 1940s and 1950s in industrialized countries with established health services and an insured vaccine supply. According to the CDC:

By 1959, ... smallpox in the Americas was endemic (only) throughout South America. Smallpox had been eliminated in Europe and most of the North African countries as well as Japan, the Philippines, Malaysia and French Indo-China. However, major epidemics continued to occur throughout densely populated India, Pakistan, Bangladesh, and Indonesia. Most countries in sub-Saharan Africa were effectively without control programs. In all, at least fifty-nine countries with 1.7 billion people – 60% of the world’s population – still lived in smallpox endemic countries of the world.⁵⁰

Two important preliminary steps towards smallpox eradication were the 1950’s development of a method for production of an inexpensive freeze-dried vaccine that was heat-stable for a month at body temperature, and improvements in vaccination technique with confirmation that a single vaccination provided immunity for at least 10 years.⁵¹ Beginning in 1950, international efforts were made to establish smallpox eradication programs, initially confined to the Western Hemisphere and then expanded to address the entire world.⁵² From 1953 onwards, there were annual proposals to the World Health Organization (WHO) to undertake global smallpox eradication, but none were successful until 1958, when the delegate from the Union of Soviet Socialist Republics (USSR) presented a lengthy report about smallpox, prompted by frequent outbreaks in Russia caused by cases coming from neighboring countries in Asia. To encourage an eradication campaign, the USSR even pledged to supply large amounts of the heat-stable, freeze-dried vaccine.⁵³ In response, the WHO director-general presented a report later in 1959 recommending national smallpox eradication campaigns in every country with endemic smallpox, aimed at vaccinating 80% of the population. There was unanimous agreement with the intent of this proposal, but only minimal funding, far below the level needed to launch this kind of effort. One reason for this was the widespread conviction that eradication would require 100% vaccination, a practical impossibility in many ways, including chronic inaccuracy and under-reporting of smallpox cases. For example, in 1959, 96,571 cases of smallpox were reported, but this was later found to represent less than 1% of actual cases. Beginning that year, the WHO director-general wrote annually to each country with known endemic smallpox as shown in Figure 2.3,

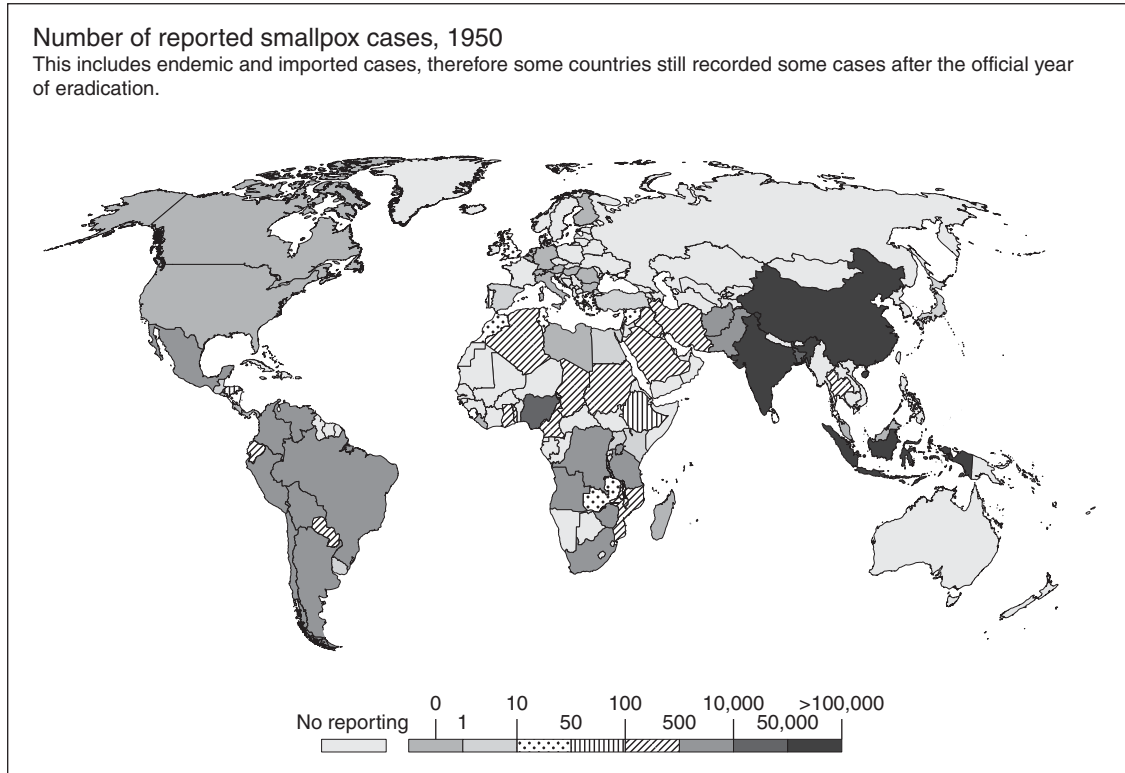


FIGURE 2.3 World map showing smallpox endemic areas in 1950.

Source: US Public Health Image Library. PHIL.CDC.gov

announcing the planned eradication program and requesting accurate reporting of cases as a preliminary to an eradication program. However, financing and staffing in support of this program remained limited and, accordingly, so was progress. Years passed with the smallpox eradication program proposal bogged down in budgetary limitations and Cold War politics.⁵⁴

Then in 1965, President Lyndon Johnson unexpectedly announced US funding for a 5-year program to eradicate smallpox and measles in West Africa, to be administered by the CDC. At that time, measles was a leading cause of death among children in Africa. The announcement was precipitated by the development of a new and effective measles vaccine which was first tested in Burkina Faso by the US Agency for International Development (USAID). The measles vaccine proved so successful that other West African countries requested similar programs, and in response, Johnson funded a new 5-year CDC-administered program. This signaled a definite shift in US support for a campaign against smallpox. In fact, US delegates to the WHO were instructed to pledge support for an international program to completely eradicate smallpox within the next decade. In response, after years of debate, consideration and re-consideration, a special budget was approved by the World Health Assembly in May of 1966 to fund a 10-year global program to eradicate smallpox.⁵⁴

Dr. D. A. Henderson, a young epidemiologist at the CDC who had headed up the USAID program in West Africa, was appointed Director of the Smallpox Eradication Unit, based at WHO headquarters in Geneva and administered through that bureaucracy. A small staff of four(!) undertook this formidable task, given the estimated annual number of smallpox cases at 10–15 million with 2 million deaths in 43 countries that spanned the globe.⁵⁵

Henderson developed a two-component strategy based on epidemiologic principles: mass vaccination of all available subjects to directly reduce the number of susceptible people and prevent disease spread; and isolation of victims and vaccination of all their known contacts by development of a reporting–surveillance system with response teams who would investigate disease reports, identify and quarantine victims and vaccinate all their contacts, thereby containing outbreaks – an approach now known as ring vaccination. Specific characteristics of the smallpox virus made this eradication strategy plausible: humans are the only victims and there is no subclinical disease – every infected person displays the characteristic rash and therefore every case can be identified. In addition, 80% of those who have been vaccinated have a permanent scar and can also be readily identified. In addition, the freeze-dried vaccine could be stored without refrigeration for up to a month, a critical factor for eradication teams in tropical countries.⁵⁶

The program began in January 1967 using mobile vaccination and surveillance teams because of inadequate existing infrastructure in most countries with endemic disease. The use of surveillance to identify and quarantine smallpox cases and initiate the containment strategy by vaccinating all contacts was a new approach to smallpox eradication efforts and fortuitously, it proved to be dramatically successful

just as the program began. Right out of the box, a test case occurred in East Nigeria in late January 1967 when initial vaccine supplies were limited so the mass vaccination approach was impossible. The team shifted to the surveillance–containment approach, using an existing missionary reporting system to identify areas with active cases, isolate victims and prioritize vaccination to contacts in those places. Amazingly, smallpox transmission was completely interrupted within 6 months. With this dramatic success, the surveillance–containment approach was validated and became the major strategy of the eradication program. This early success in Nigeria heralded a series of successful programs culminating in eradication of smallpox in West Africa in May 1970.⁵⁷

Despite a long list of problems including recruitment and training of completely inexperienced teams, variable vaccine supplies, country-specific political demands, repair and maintenance of mobile unit vehicles, substandard vaccine quality, diplomatic challenges, monsoon floods and devastating drought, war, political corruption and communication barriers, the Smallpox Eradication Unit forged ahead, establishing teams in every one of the countries with endemic disease by 1971. The next successes were in South America and Indonesia, where smallpox was eradicated by March 1971 and April 1974, respectively.⁵⁸

India, Pakistan and Bangladesh proved to be especially challenging. At the beginning of the program, they accounted for more than half of all reported smallpox cases. The disease was so pervasive that India even had its own Hindu goddess of smallpox, Sital Mara. Despite substantial national effort and international leadership and support, smallpox persisted unabated in central India. Special field teams were created to aggressively implement the surveillance–containment program, using village-by-village and then house-by-house searches. Ultimately, a veritable army of public health workers was deployed to identify and quarantine every case of smallpox and vaccinate every contact. After a formidable team effort, smallpox was eventually eradicated from India by June 1975 and Bangladesh by January 1976.⁵⁹

Ethiopia and Somalia were the last smallpox strongholds. Fueled by public rejection of vaccination, severe drought and famine, and civil disorder, in a large country with roads and bridges in terrible condition, an effective attack on smallpox eventually required the use of helicopters, which ultimately eliminated the disease in Ethiopia by July 1976. Somalia shared a long, open border with Ethiopia and its highly mobile nomadic population made disease detection extremely difficult. In addition, the Somali government was actively obstructive. Despite these obstacles, the last case of naturally acquired smallpox in Somalia – and in the world – occurred in October 1977.

The Smallpox Eradication Program was ultimately declared successful at the end of December 1977. This was followed by a two-year international surveillance program before the WHO declared smallpox to be completely eradicated on May 8, 1980. Remarkably, the Smallpox Eradication Unit, led by their extraordinary director, D. A. Henderson, had achieved what many thought to be an impossible goal in only 10 years.^{50,60}

The Post-Eradication Era: Smallpox as a Biological Weapon

The world's last case of smallpox actually occurred after the international campaign ended. In August 1978, a medical photographer named Janet Parker at the University of Birmingham in England fell ill with fever and a hideous rash. Two weeks later, when she was already critically ill, she was diagnosed with smallpox. She contracted the virus via an air duct from a smallpox research laboratory on the floor below her own office. Ms. Parker died and the director of the smallpox research laboratory committed suicide. This incident reinforced the deadly capacity of smallpox at a time when there were smallpox virus stocks in at least 75 research laboratories around the world. After this incident, many countries called for destruction of all stocks of the virus. In 1980, as part of the declaration of eradication, WHO mandated that only the CDC Centers in the United States and the Research Institute for Viral Preparations in the USSR be allowed to retain a limited supply of the virus in high-security laboratories.⁶¹

To this day, debate continues over whether the American smallpox virus reserve should be retained for theoretical research purposes or destroyed because of the threat posed by possible escape of the virus. Scientists continue to call for complete destruction of the virus. When gene sequencing techniques developed, it was proposed that all smallpox virus stocks be destroyed once several different strains of the viral genome were sequenced – this proposal was endorsed by the United States and Russia, but when the sequencing goal was reached in 1994, the US Department of Defense objected. Despite continuing recommendations from the global scientific community and formal review every 3–4 years by a WHO Advisory Group of Independent Experts (most recently in 2018), the American smallpox virus stock has never been destroyed.⁶²

The smallpox reserve introduces the second chapter of the smallpox story: smallpox as a potential biological weapon. A biological weapon is defined as a harmful biological agent such as a pathogenic microorganism or a neurotoxin used as a weapon to cause death or disease, usually on a large scale. Since the declaration of smallpox eradication in 1980, the general population has not been vaccinated against smallpox, which means that accidental or deliberate release of the smallpox virus could have devastating consequences for our now unprotected and highly mobile global population.⁶³

Historically, smallpox has already been used as a biological weapon, perhaps most famously in 1768 during the French and Indian Wars when invading British soldiers under the direction of Lord Jeffery Amherst gave blankets from smallpox victims to North American Indian tribes, initiating massive epidemics with high mortality.¹¹ Smallpox was also used very effectively by the British Military during the US Revolutionary War until George Washington had all of his troops vaccinated. No doubt there were many other instances when bioweapons like smallpox were used without historic documentation. In 1928, use of biological weapons was formally addressed by the Geneva Protocol, which was drawn up and signed by all participants under the auspices of the League of Nations, with explicit prohibition

of the use of chemical and/or biological weapons in war.⁶⁴ Despite this prohibition, there were active bioweapons programs in many countries, dating from as early as the 1930s.

Japan was the first country known to be considering germ warfare when it initiated a massive program after World War I. Led by Major General Ishii Shiro and by decree of Emperor Hirohito, multiple biological warfare sites were established by the late 1930s. Using established pathogens like smallpox, anthrax and the plague, the Japanese focused their research on methods for mass exposure. Their most famous bioweapons site, Unit 731, developed balloon bombs for dispersion of pathogens by airplane and plague bombs to be transported by submarine. According to news reports in 1939, Shiro's team actually dispatched an airplane to spread *Yersinia pestis*, the bacteria that causes the bubonic plague, during the Japanese–Soviet war using infected fleas – the dispersal caused a localized outbreak of the plague that killed 22 Chinese citizens.⁶⁵ Among other techniques, the Japanese biowarfare team developed a bomb to inject anthrax-coated shrapnel and a radio-controlled bomb cluster designed to create a cloud of bacteria just above the ground.⁶⁶ After the surrender of Japan that led to the end of World War II, Shiro and members of his Unit 731 were investigated by US scientists and their research and manufacture of germ bombs, techniques of mass production of bacteria and their bio-warfare experiments were discovered. Their records included horrific descriptions of testing on human subjects.⁶⁷ Incredibly, the Japanese scientists were reportedly exonerated from being sued for war crimes in exchange for their “human experimentation” data, which was considered valuable information for microbiology and disease pathogenesis. Regardless of the ethics of this decision, the Japanese bioweapons program is thought to have ended at the end of World War II, although it is impossible to be sure of this.

From Russian defectors, we know that the Soviet Union also initiated its biological weapons program in the 1920s, despite the fact that the USSR was a signatory to the 1925 Geneva Convention.⁶⁴ Original efforts focused on weaponization of known pathogens, and according to Colonel Kanatzhan Alibekov, known in the USA as Ken Alibek, a colonel in the Russian bioweapons program who defected to the United States in 1992, the Soviet Union aerosolized *Francisella tularensis*, the bacteria that causes tularemia, and used it against German troops in 1942; details of this effort and of the entire program are contained in Alibek's book.⁶⁸ As he describes it, the Soviet program accelerated during the Cold War, and ultimately, there were reportedly more than 50 different research facilities which weaponized and stockpiled multiple bio-agents. These included smallpox, for which a specific factory was created near Moscow in 1947. According to Alibek, the smallpox program used a highly virulent strain of smallpox from India which they developed for delivery in an aerosolized form. A production line to manufacture smallpox on an industrial scale was launched with the *Variola major* virus stockpiled in large quantities throughout the 1970s and 1980s.⁶⁹ This effort occurred despite the apparent wholehearted participation of the USSR in the WHO global campaign to eradicate smallpox. To our knowledge, the Soviet weaponized smallpox was never released,

but its destination remains uncertain. Over time, the Soviet bioweapons effort grew into an enormous program, combining multiple institutions under different ministries with commercial facilities, collectively known as the Biopreparat after 1973. The Biopreparat pursued offensive research, development, and production of biological agents as if it was legitimate biotechnology research. Annualized production capacity for weaponized smallpox, rabies, and typhus combined was reported to be 90–100 tons.⁷⁰

By the 1980s, the Cold War was at its height. According to Alibek, the USSR believed that war between the superpowers was likely and the work of the Biopreparat was focused on that inevitability. The massive clandestine bioweapons program developed an exceptionally dangerous aerosolized form of anthrax, which was accidentally released from a secret bioweapons facility in the Soviet city of Sverdlovsk in April 1979. Propelled by a slow wind, the anthrax cloud drifted south-east, producing a 50-kilometer trail of disease and death. At least 66 people died, making this the deadliest recorded human outbreak of inhalation anthrax. A study published subsequently in the journal *Science* in 1994 concluded that the geographic pattern of the outbreak clearly showed that it was caused by an aerosolized form of anthrax released from the local Soviet bioweapons facility.⁷¹ When Ken Alibek was a bio-weaponeer – his own term – in the Soviet Union, he was involved in development of a method to produce anthrax in huge quantities in a form that could be loaded onto cruise missiles and delivered to targets in the United States without advance warning. He reports this had been accomplished by 1987.

The fall of the Berlin Wall, the shredding of the Iron Curtain and the end of the Cold War were followed by the dissolution of the Soviet Union. In September 1992, Russia signed an agreement with the United States and Great Britain, promising to end its bioweapons program and to convert its facilities for benevolent scientific and medical purposes.⁷² Compliance with the agreement and the fate of the former Soviet bio-agents and facilities are, however, still largely undocumented, with no visible campaign to dismantle the residual elements of the program. US security analysts have raised the possibility that Soviet bioweapons could have fallen into the wrong hands. Ken Alibek believes that, following the collapse of the Soviet Union in 1991, disaffected scientists could have clandestinely sold samples of biologic agents like smallpox or moved the program to rogue states to continue illicit biological weapons development. In their comprehensive book, Leitenberg and Zilinskas describe the full scope of the USSR's offensive biological weapons research and report that the means for waging biological warfare could well persist in Russia today.⁷²

Meanwhile, the United States developed its own extensive bioweapons program beginning as early as World War I when tests of two methods for dissemination of ricin, the deadly by-product of castor beans, were conducted; neither delivery method was perfected before the war in Europe ended. To this day, there is no antidote for ricin toxicity. Although this early American effort was unsuccessful, it signaled the serious early intent of the military to develop bioweapons. When

World War II erupted, the official US government position was that biological weapons were impractical, and as late as 1941, the US had no biological weapons capability despite knowledge of the growing offensive programs in Russia and Japan. President Franklin Roosevelt approved development of a biological warfare program in November of 1942 and in response, the US Army Biological Warfare Labs were established at Fort Detrick, Maryland in the spring of 1943. Within 6 months, a high-security biological weapons facility was completed, followed by construction of multiple satellites. Galvanized by reports that the Germans were preparing a pilotless biological weapon for use against the Allies, the American team coordinated with Canada and Britain to develop bombs to be filled with anthrax spores that could be dropped from planes. While safety testing was still going on, the United States dropped the atomic bomb on Hiroshima and that ultimately led to the end of the war. Germany was subsequently found to have no weapons systems for delivery of biological weapons.⁷⁴

During the Cold War, the United States biological warfare program expanded into a military-driven research program with the focus on delivery of biological weapons in multiple settings. The Detrick team established a Special Operations unit to evaluate the contamination of clouds with biological weapons. Working with the British, they conducted simulated open-air germ raids in the Caribbean using anthrax spores and *Pasturella tularensis* as agents, and monkeys and guinea pigs as experimental victims. Over the next decade, right through the Korean War, the American bioweapons program continued to investigate the delivery of airborne pathogens. The program included the use of human subjects, Seventh-Day Adventist soldier volunteers who were sprayed with the agents that cause “Q fever, tularemia, typhoid fever, Eastern, Western and Venezuelan equine encephalitis, Rocky Mountain spotted fever and Rift Valley fever” either after vaccination or with treatment to prevent development of the disease.⁷⁵ In 1956, as the deployment of a biological weapon appeared more and more feasible, the National Security Council adopted a special directive stating that the United States was prepared “to use bacteriological weapons in general war” under the direct orders of the President.⁷⁶ When Kennedy became President, a major new biological weapons program began, with a shift in approach from biological agents aimed to kill to those that would incapacitate. Throughout, research focused on dissemination of known disease agents like smallpox via options such as spray generators hidden in briefcases for use in crowded public areas and aerosol sprays delivered by military jet planes. By the summer of 1968, field trials established that the United States had proven technology for effective delivery of biological weapons.⁷⁷

The controversial Vietnam War brought public awareness of the US biological weapons program. The use of chemicals, riot-control agents, and herbicides such as Agent Orange drew national and international criticism. Information about the American bioweapons research program was released to overwhelmingly negative public opinion. In response, then President Nixon issued his “Statement on

Chemical and Biological Defense Policies and Programs” on November 25, 1969 in a speech from Fort Detrick:

The United States shall renounce the use of lethal biological agents and weapons, and all other methods of biological warfare. The United States will confine its biological research to defensive measures such as immunization and safety measures.⁷²

The statement ended, unconditionally, all US offensive biological weapons programs and led to signing of the Biological and Toxin Weapons Convention by the United States, the United Kingdom and the Soviet Union in 1972. Nixon ordered all US biological weapons research to be confined to defensive purposes and the destruction of the existing biological arsenal; this is thought to have been accomplished over the next several years, with the notable exception of the smallpox reserve.⁷⁸ Ultimately, despite more than 30 years of research and billions of dollars in funding, the United States has never been known to employ offensive biological weapons.

Over the next two decades, American efforts focused on bioweapon defense. The United States is said to have believed that all other international bioweapons programs had been eliminated. As we know from the reports of defectors, however, far from abandoning its bioweapons program, the Soviet Union had intensified it with their “civilian” pharmaceutical company Biopreparat functioning as a front for a massive offensive bioweapons program well into the 1990s.⁷⁰ As part of Operation Desert Storm, the US war with Iraq in 1990–1991, intelligence reports revealed that Iraq had a biological warfare program that had begun in the 1970s. By 1991, Saddam Hussein was reported to regard his biological warfare program as a critical part of his arsenal of WMD, authorized for use against the US. No biological weapons were utilized during Desert Storm, but covert bioweapons research continued in Iraq after the war until 1995 when the program was reportedly abandoned.⁷⁹ Over time, evidence that bio-warfare efforts were alive and well around the world has accumulated. According to a 1995 report by the US Office of Technological Assessment, there were at least 17 nations known to possess biological weapons at that time: Libya, North Korea, South Korea, Iraq, Taiwan, Syria, Israel, Iran, China, Egypt, Vietnam, Laos, Cuba, Bulgaria, India, South Africa, and – last but not least – Russia.⁸⁰ Under President Clinton, attempts were made to increase the American biodefense program, including plans to vaccinate all military personnel against anthrax, increase surveillance for bioweapons, augment public health readiness against bioweapons attack and stockpile vaccines and disease antidotes, but a coherent biodefense program never developed.⁸¹

9-11-2001

The terrorist attacks on the United States on September 11, 2001 followed by the delivery of anthrax powder to American journalists and politicians associated with 22 infections and five deaths described in the introduction to this chapter initiated

a new era of intense American concern about bioterrorism. The CDC categorizes smallpox as a Class A bioweapon, the highest category, along with anthrax, botulism, plague, tularemia, and viral hemorrhagic fever viruses like Ebola. The threat of an aerosol release of smallpox is considered a clear and present danger, with a single case of smallpox designated as a WHO “public health emergency of international concern.”⁸²

In the immediate post 9/11 atmosphere, the 2002 White House budget requested 11 billion dollars over two years to “enhance national protections against biological terrorists.”⁸³ Former President George W. Bush signed the Project BioShield Act in 2004 to accelerate research, development, purchase, and availability of medical countermeasures against chemical, biological, radiological, and nuclear agents. With specific reference to smallpox, the Advisory Committee on Immunization Practices (ACIP) of the CDC developed new recommendations for smallpox pre-vaccination of designated healthcare teams at every acute care hospital in the country. In the event of a bioweapons attack with smallpox, these teams of vaccinated individuals were designated to provide continuous care of suspected smallpox cases for the first 48 hours until additional healthcare workers could be vaccinated. The ACIP recommendations, published in 2003, provided detailed instructions on the composition of the smallpox care teams and the prevention of disease transmission.⁸⁴ After 2008, the recommendations were updated with the freeze-dried vaccine, Dryvax, replacing the live smallpox vaccinia vaccine, ACAM2000, for protection of at-risk individuals.⁸⁵ Between December 2002 and October 2009, more than 1.8 million US service members received smallpox vaccinations.

Globally, emergency supplies of smallpox vaccine were dramatically increased after 9/11. There is a physical stockpile of smallpox vaccine held at WHO Headquarters in Switzerland, composed of calf-lymph smallpox vaccines from a variety of sources dating from the final years of the eradication program, estimated to consist of ~2.4 million doses. In addition, there is a pledged stockpile held by multiple donor countries in their respective national stockpiles for use in time of international need. In the United States, the ACIP recommends routine smallpox vaccination for specific populations at high risk of occupational exposure to orthopoxviruses. The FDA has approved two new vaccines for stockpiling based on safety profile and proof of generated immune response to be used for such individuals.⁸⁶ ACAM is a replication-competent vaccine which contains *Vaccinia Ankara*; the vaccine does not contain the variola virus and cannot cause smallpox, but it can cause a vaccine-related infection which is usually mild. The live, infectious vaccinia virus can also be transmitted from the vaccine recipient to unvaccinated persons who have close contact with the inoculation site. The risk of side effects in contacts is the same as those for the vaccine recipient so the vaccination site requires special care to prevent virus spreading. In 2019, the FDA licensed a new vaccine, trademarked JYNNEOS, but also known by the brand names Imvamune and Imvanex. This is an attenuated live vaccine for the prevention of smallpox and monkeypox. As a replication-deficient vaccine, it cannot cause infection and can be used for vaccination of people with immune deficiencies.⁸⁶

After 9/11, the subject of treatment for smallpox was revisited. Animal studies suggested that the antiviral drug cidofovir might be a useful therapeutic agent. Cidofovir was the first nucleotide analogue approved for clinical use and has demonstrated *in vitro* activity against poxviruses; its clinical utility is unknown. It is given intravenously with careful monitoring of kidney function. Specific application in smallpox infection has not been investigated.⁸⁷ The US government has stockpiled 2 million doses of the antiviral medication Arestvyr, an egress inhibitor which prevents the formation of extracellular enveloped forms of orthopoxviruses, to be used in exposed individuals in combination with the smallpox vaccine in the event of a smallpox bioterrorist attack. Tecovirimat is an oral antiviral drug for orthopox viruses which inhibits the function of a major envelope protein required for the production of extracellular virus.^{88,89} Theoretically, it could be combined with smallpox vaccine to maximize disease suppression after exposure to the virus. For obvious reasons, it has never been tested in humans, but more than 90% of monkeys and rabbits that were infected with a virus similar to smallpox and then given the drug survived. In August of 2018, the FDA approved TPOXX, a commercially developed version of tecovirimat to treat smallpox. TPOXX has now been added to the American emergency stockpile for biodefense against smallpox, with 2 million doses delivered to the US government to be added to the stockpile as part of the emergency biodefense reserve.⁸⁹

Looking Back :: Moving Forward

In the rush of concern about bioterrorism, it is easy to forget the early history of smallpox – how this dreaded disease haunted populations all over the world with disfigurement and death for more than five centuries, well into the 1900s. Richard Preston reports that “In the last hundred years of its existence, smallpox ... killed at least a half a billion people.”⁹⁰ It is easy to forget the efforts of ordinary citizens like Lady Jane Montague and of scientists like Edward Jenner which resulted in development and acceptance of an effective vaccine. The struggle to prevent the disease – first with variolation and then with vaccination – was dramatically successful, the first completely effective prevention program in world history. There are critical characteristics of the smallpox virus that made eradication possible and that bear repeating in terms of future eradication efforts: the virus is stable with little spontaneous mutation over time; humans are the only victims and there are no subclinical cases of smallpox meaning no infected individuals will be missed; the existing vaccine, available in a freeze-dried form, is safe and highly effective. And the Smallpox Eradication Program was a model of how a knowledgeable and determined leader can empower thousands of committed workers all over the world to complete a single critical task. D. A. Henderson used his knowledge of epidemiology to design the technique of ring vaccination in which every case of smallpox was quarantined and every known contact of each case was sought out and vaccinated. Effectively, this technique created a wall of immunity around areas of active disease, preventing the spread of smallpox and allowing the virus to

die off – this technique has since been used to effectively vaccinate against Ebola. By eliminating layers of bureaucracy and authorizing teams of local village health workers to perform the critical work of searching for and reporting smallpox cases, Henderson created superbly effective surveillance teams all over the world. Inspired by his tireless dedication and flexible leadership, smallpox was eradicated from the face of the earth – a singular, remarkable triumph. There is still much to be learned from the history of smallpox eradication.

That should have been the end of the smallpox story. It could have been the end of the smallpox story. But instead of destruction of all existing *Variola* virus reserves, the World Health Organization recommended that special collaborating centers be created to “hold and handle stocks of *Variola* virus.”⁹¹ Per that recommendation, we know of at least two remaining stocks of the live smallpox virus, one at the CDC in Atlanta and one at the Research Institute for Viral Preparations in Moscow. These two reserves are being maintained despite the enormous risk inherent in accidental release of the smallpox virus, and subsequent sequencing of the virus allowing the genetic blueprint to be safely preserved indefinitely. There is persistent concern about the deliberate use of smallpox as a bioweapon – the Russian defector, Ken Alibek, describes 40 years of Soviet research that included a production line capable of manufacturing 80–100 tons of liquid, weapons-grade smallpox virus per year: one teaspoon of this smallpox preparation could in theory infect every person on the planet.^{92,93} The Russian bioweapons program reportedly even had plans to develop a more deadly hybrid virus, a combined smallpox/Ebola agent using molecular genetic techniques.

Internationally, there is evidence that development of biological weapons is ongoing. According to the US Department of Defense, countries including China, Egypt, Iran, Israel, North Korea, Russia, and Syria continue to develop biologic weapons, despite the fact that most are signatories of the 1972 Biological Weapons and Toxins Convention treaty.⁹⁴ Assumed possessors of biologic weapons like Iran, North Korea, and Syria are suspected of sponsoring and harboring terrorist groups like Al-Queda and the splinter groups that compose ISIS, where development of biological weapons represents a terrifying potential source for terrorism.

There are no records documenting the use of biological weapons in warfare since 1972, but their use as a tool of terror emerged dramatically after 9/11 when the US was threatened by the spread of anthrax spores. This incident put the threat of biologic weapons at the top of national and international security agendas and emphasized the need for contemporary reinforcement of the Biological Weapons and Toxins Convention treaty. Interviewed in 2016, Tom Ridge, the first US Secretary of Homeland Security said:

... one of the most significant gaps, in my judgment is bio-defense. I mean, face it, (9/11) was 15 years ago, and yet we still don't have a (consistent bioweapons) strategy. I think that one of the most serious, long-term threats from any source, is in the biological area. And 15 years after anthrax, we're

still struggling to have a strategy and to operationalize a capability to respond quickly with a vaccine and recover from an incident ... with a contagious pathogen. It's a real problem.⁹⁵

In this age of terrorism, when the threat of biological weapons hangs over our increasingly vulnerable planet, the history of smallpox is both a major success story and a powerful cautionary tale.

HISTORIC PERSPECTIVE

VACCINATION: RACE AND RELIGION

The eradication of smallpox in 1980, with the exception of two known stores maintained in government laboratories in the United States and Russia, is considered one of the greatest public health victories of the modern world. Smallpox devastated populations beginning in the ancient world, where skeletons entombed in Egypt still show the scars left by this vicious virus. It has a relatively high mortality rate of 30% with higher rates of long-term disability, including blindness and scarring. It is also highly contagious, so the fact that it was eliminated from the world through the concerted application of vaccination reflects the tenacity of public health efforts in the face of even the most aggressive viruses. While it seems logical to use vaccination to end a disease that cost billions of lives between the first ancient outbreak and the final recorded case in 1977, it actually caused serious debates in the early modern world when inoculation (which preceded vaccination) first proved to be effective. This section focuses on the seventeenth-century religious debates that occurred in the United States and in other Protestant countries over the relationship between divine will and disease. While this might seem like a uniquely early modern debate, its echoes are heard today in the refusal by people of some faiths to accept some forms of medical treatment, such as Jehovah's Witnesses who will not accept transfusions, and those who reject vaccinations on religious grounds, such as Christian Scientists and the Dutch Reformed Church. The issue of refusing vaccination on religious grounds has never been more relevant: increasingly, parents are opting out of vaccinating their children, and they are using religious grounds for that refusal. Forty-seven states allow this practice, and parents are not required to provide proof that their basis for refusing vaccination is, in fact, religious.⁹⁶ While antivaccination propaganda inaccurately portrays vaccinations as the cause for autism and other developmental disorders, it simultaneously ignores the reality that vaccinating less than a high proportion of a population will permit epidemics to re-emerge. The rise of small outbreaks of measles, mumps, and other previously eradicated (in North America) childhood killers demonstrates the critical importance

of vaccination. Perhaps a look at early modern religious debates over smallpox immunization will help to clarify our current situation.

Inoculation is the practice of taking pus from the pox of an infected patient, scoring an uninfected person's arm, and placing the pus directly over the scoring. The practice was widely used in China and the Middle East before being imported to England and then North America through the efforts of Lady Mary Wortley Montague, an English aristocrat who had been badly disfigured by smallpox and lost her brother to it. She was married to the English ambassador to Turkey, where she encountered the procedure and observed that it caused a much less severe case of smallpox to occur in the recipient individual but still conferred immunity. She inoculated her own children and was a major force in introducing the practice to the English aristocracy upon her return home. Inoculation carried risks, including the potential for starting a new epidemic and the death of the inoculated patient, but it was a far more effective solution than any other available before Edward Jenner's vaccine. The debate over whether to inoculate rested not in any question about whether inoculation was successful in preventing smallpox or on its potential dangers. Instead, it lay in the interpretation of disease as part of divine will. For some Protestants, if God sent a virus to assail his followers but there was a known preventative or cure available, it was immoral not to use it. For others, accepting suffering was a means of demonstrating faith, and disease was a test of faith given by God. In 1583, for example, a physician who wrote to magistrates about the use of natural remedies to protect against or treat the plague during an epidemic warned against trying to protect oneself in opposition to divine will, stating if anyone of "conscience and religion shall be persuaded to think that he resisteth the will of God, [or] if by the help of man he labor to avoid his punishment, he must suffer himself to be better taught."⁹⁷ Susan Emlen, a Quaker woman in 1814 Philadelphia afflicted by breast cancer who chose to have a mastectomy (a rare procedure at that time, done without anesthesia and having significant complications), wrote of her spiritual understanding of her cancer in letters to her father and husband. She repeatedly referred to her cancer as a trial for her soul sent, in a quote from Lamentations, by a gracious power "who afflicts not willingly."⁹⁸ Note that despite her deep religious calling and spiritual comprehension of her cancer, Emlen sought the most aggressive treatment possible, perhaps in part because her brother-in-law was "the father of American surgery," Phillip Physick, who held a medical degree from Edinburgh and had practiced for three years under the renowned London surgeon John Hunter.⁹⁹ Emlen, supported by her surgeon and husband, saw no conflict between seeking every possible solution for her cancer and experiencing her spiritual trial. A century before Emlen was diagnosed, however, Boston saw a heated contest between religious and medical authority and

different interpretations of Protestantism in the context of a debate over smallpox inoculation.

The Reverend Cotton Mather was the proponent of smallpox inoculation in this case, which occurred during the smallpox outbreak of 1721. It was a major outbreak, in which 6000 cases were reported in a city of 11,000 people, and the mortality rate was 14%. This was the deadliest smallpox outbreak in New England of the seven that occurred during the first half of the eighteenth century.¹⁰⁰ Mather was a member of the Royal Society with a strong interest in natural philosophy and the traditional understanding that clergy are responsible for the health of their flock's bodies as well as their minds. As a result, he maintained a healthy interest in medicine, although he had no formal training in it. In 1716, he wrote the Royal Society to indicate that he had read the article in the *Transactions* discussing smallpox inoculation in Turkey, but he also asserted that he had already heard of this procedure through a discussion with his African servant, Onesimus, who had been inoculated before being transported to the Americas. Mather confirmed Onesimus' account by querying other Africans about the practice, and upon learning that it was effective, became a strong proponent of the procedure. When smallpox hit Boston again, he found a doctor, Zabdiel Boylston, to help him inoculate volunteers. Mather believed inoculation was a divine gift sent to help save lives and ignoring it would be tantamount to rejecting divine assistance, but he also seemed very interested in the practical applications of the practice. His efforts were most vociferously countered by the physician William Douglass, who remained convinced that inoculation was ridiculous on two fronts: first, because Mather's trials were based on the report of an African servant and a Royal Society article about a practice in the Middle East, and he did not value knowledge generated in non-European contexts, and second because he feared it would only hasten the spread of smallpox by exposing more people to it and creating more cases. Douglass was one of the few practicing medical men in Boston who actually held a medical degree, and historians have attributed some of his resistance to the inoculation trial to an effort to establish authority over medical practice at a time when the profession was dominated by people without university training. Douglass' racialized perspective on which people could produce valuable knowledge were typical for his time, as was his urge to defend his professional territory.¹⁰¹ Mather, on the other hand, was a bit of a maverick, as he combined his traditional area of knowledge with his deep passion for natural philosophy and medicine. While Mather and Boylston were brave for putting their reputations on the line to defend inoculation, it is the volunteers who truly deserve recognition. Two hundred eighty-seven individuals chose to be inoculated, and not much is known about their backgrounds or what drove their decision. What is known, however, is that the mortality rate among

those who were inoculated was 2%, a remarkable relative risk reduction, compared with the overall mortality rate for that outbreak.¹⁰² Mather and Boylston's use of the most sophisticated study design available, employing control and experimental groups, underlined the validity of their results and encouraged other practitioners in New England to adopt inoculation. It also damaged the ongoing argument that all diseases occurred differently in people of different races, putting an early nail in the coffin of racial medicine. Mather and Boylston's efforts were perhaps the first North American clinical trial, and they proved critical to the adoption of inoculation in the colonies.

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3

YELLOW FEVER

The Jungle Story

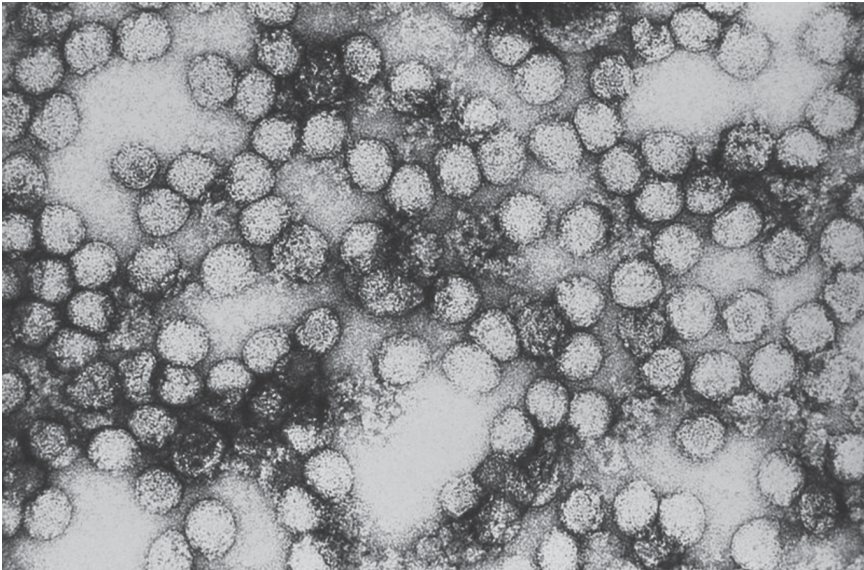


FIGURE 3.1 Electron micrograph of yellow fever virus.

Credit: Alamy/CDC/BSIP.

MOSQUITOES LOVE ME

Mosquitoes love me. A huge group can be sitting around at dusk having a lovely time but only I will be surrounded by a swarm of happy mosquitoes. This was never such a big deal until my sister Sarah moved to Venezuela and invited us to visit. Sarah has been an adventurous traveler since she was a teenager. She and her husband moved first to Ethiopia when he joined CIDA, the Canadian International Development Agency, the federal government agency that administers the official program for developing countries. Originally it was just the two of them moving from one post to another, but by the time they moved to Venezuela, they had two young daughters, a 5-year-old and a newborn. The 5-year-old is the closest thing my own daughter has to a sister and the move to South America had been a painful separation, so we excitedly planned a trip over winter break.

It was 1986. Allison was 8 years old and this was her first passport: I still have it, that sweet innocent face with a superimposed official cancellation stamp. Sarah warned us about travel requirements so we went to the Travel Clinic at the university medical center where I worked. Reams of material from the CDC outlined an alarming list of dangers. There was no safe drinking water so bottled water was recommended for all intake. Malaria was prevalent so we needed drug prophylaxis plus insect repellent and mosquito nets. No vaccinations were required and I don't recall any mention of yellow fever. However, even then, the State Department warned "violent crime ... is pervasive in Venezuela, both in the capital Caracas and throughout the country. Heavily armed criminals are known to use assault rifles to commit crimes at banks, shopping malls, public transportation stations, and universities." Assault rifles! I was shocked: Caracas was the site of the Canadian embassy where my brother-in-law worked and the destination of our flight. I called my sister. She agreed that crime was an issue, but reassured me that their community was completely safe. Reassured – after all, she and the girls *were* living there! – we arrived in Caracas in the middle of February, pre-loaded with quinine.

We landed at night at the Simon Bolivar International Airport outside the city, with the runways paralleling the ocean front. Caracas is in a river valley about 10 miles away with low mountain peaks on all sides. The family Volvo 4 × 4 climbed up and up and then down into the city. It was much grander than I expected, with blocks and blocks of skyscrapers interspersed with patches of luxuriant vegetation. There was no sign of crime on the streets and absolutely no sign of mosquitoes. Their townhouse was gorgeous with dark Brazil wood floors, huge tropical plants and white upholstered furniture throughout. But there *was* evidence of insect life: that first night, I went down to the kitchen for a bottle of water and when I turned on the light, a dozen huge cockroaches as big as dinner plates scuttled for cover. If there are mosquitoes, I thought, they

are going to be massive. The next day, we swam at the Caracas Country Club and then had lunch on the terrace of a hotel, all very posh – but around the perimeter, security guards with machine guns paraded throughout our meal. I thought: Danger: Check; Security: Check.

The next day we headed east to Playa Cumana, a beach resort east of Caracas. Once out of the city, we were driving in dense jungle over very rudimentary roads. The car pitched from one turn to the next, lurching upright only to dive into another corner. An hour or so into the trip, I heard a small voice from the back of the car: “Mummy?” I looked back to see Allison’s white, agonized face. “Are you carsick?” The car jerked to a stop and we jumped out, literally on the edge of the jungle. I was holding Allison’s hair out of the way and patting her back when the mosquitoes found us. A dense, black swarm of huge mosquitoes whined and whizzed around our heads, landing on every inch of exposed skin. Swatting and slapping, we scrambled back into the car carrying several dozen mosquitoes with us. The car was pandemonium as we tried to eliminate every one. Moving on at last, I thought, Mosquitoes: Check; and then – this could be a disaster.

But the beach resort was incredible – a row of small cottages at the edge of the most beautiful beach I have ever seen: soft, pure white sand and turquoise-green waves drifting towards the shore. Standing at the edge of the ocean, the beach stretched out as far as you could see in either direction with not a single thing in sight. We ate at a big picnic table shaded by pairs of giant coconut palms. The ocean off the shore was shallow and the girls ran in and out of the waves while the grown-ups took turns as lifeguard. At night, we fell asleep to the sound of the waves. And there were no mosquitoes. Yes, Allison and I were studded with itchy bumps, especially on our arms and legs and the backs of our necks, but there were no new mosquitoes – and by the time we left, the bites were starting to recede. All these years later, I still remember that as a perfect, golden time.

From there, we flew to Angel Falls, the world’s highest uninterrupted waterfall, dropping almost a thousand feet from a table-top mountain in south-east Venezuela. Considered the eighth wonder of the world, Angel Falls are not easy to reach, requiring a special flight from Caracas to a tiny airport in Canaima. On the way in, the pilot zoomed in close and tilted the plane way over so we could glimpse the spectacular fall of water from the air before we landed. Canaima itself perches on the edge of a base camp, the starting point for river trips to the falls. We travelled up river by motorboat and then hiked up to where we could see the falls, a narrow cascade of water shooting out from a cleft at the top of the mountain and falling straight down a vertical cliff face. At the bottom, the water strikes with such force that it sounds like a continuous thunder roll and the base is continuously shrouded in a cloud of water vapor. It is beyond spectacular.

But it's the night I remember most. We were all staying together in a basic concrete shelter with no electricity. There were screens on the windows but we were told to also use mosquito nets which hung from the ceiling over each cot. Lying under my net in absolute blackness, the sound of the jungle was overwhelming, a palpable force filling the room. There was a loud constant hum composed of many sounds – chirps, rustles, knocks, warbles. And over everything, there was the continuous electric whine of mosquitoes. The noise was so intense I did not fall asleep for many hours. But in the morning with the bright hot sun overhead, the jungle sounds were hardly noticeable. On our way to breakfast, we saw gorgeous parrots in the trees around the compound and orchids growing wild. I saw no mosquitoes. But back in the Jeep headed for the airport, I realized in a way I never had before that mosquitoes are a formidable force.

Historically, mosquitoes date back to Aristotle in the second century BC. Called variously gnats or little flies or midges, they are described exactly as we experience them today: a small insect with long legs and delicate wings that make a persistent, whining buzz in flight and whose bites draw blood and leave itchy welts behind. Insects very similar to modern mosquito species have been found preserved in amber dating back more than 100 million years, but contemporary phylogenetic studies suggest diversion of different species more than 200 million years ago. Mosquitoes have a complex life cycle characterized by dramatic short-term changes in shape and function. Female mosquitoes lay their eggs along the edge of small pools of stagnant water – even a bottle cap filled with rain water will do. Larvae hatch with their heads down, breathing through a siphon or a pore called a spiracle in the tail. Within days, the pupa emerges and transforms into the adult insect. Completion of all three stages can take as little as 5 days. Adult mosquitoes mate only a few days after emerging from the pupal stage, the males attracted by the characteristic whine of females. After mating, the females of most species require a blood meal to provide nutrition for their eggs to mature, typically in a period of days. Once the eggs are fully developed, the female lays them in stagnant water and the process begins again.

The mosquito's head is specialized for feeding and for receiving sensory information through its long, segmented antennae which identify appropriate host odors, as well as potential breeding sites where females can lay eggs. In all mosquito species, the male antennae also contain auditory receptors to detect the whine of females. A large part of the female mosquito's sense of smell is devoted to sniffing out blood sources, but more than a third of 72 odor receptors on the antennae are actually tuned to detect chemicals found in perspiration. Many studies have attempted to define exactly why some individuals like me are so attractive to mosquitoes. A prime attractant is 1-octen-3-ol or octanol, a by-product of linoleic acid

metabolism in humans which is contained in expired breath and sweat. Apparently, female mosquitoes find certain proportions of octanol and carbon dioxide in sweat irresistible. Mosquitoes also carry a specific protein called Or4 that allows detection of sulcatone, another by-product of human metabolism. Sulcatone is a volatile odorant that exists as a miasma around us, again more prominently in some humans than others: mosquitoes and other blood-feeding insects use the scent of sulcatone to hunt us down. Apparently, use of this miasma as a tracking device is especially true for certain mosquito species.

During blood feeding, mosquitoes inject saliva containing any pathogens they are carrying along with an anticoagulant to prevent blood clotting. Mosquito-borne diseases cause millions of deaths worldwide every year with a disproportionate effect on children and the elderly in developing countries. Three mosquito species bear primary responsibility for the spread of human diseases: *Anopheles* mosquitoes are the only species known to carry malaria as well as filariasis/elephantiasis and the viral encephalitides; *Culex* mosquitoes also carry filariasis and the encephalitides plus the West Nile virus; and *Aedes* mosquitoes carry dengue, chikungunya, Zika, encephalitis and yellow fever ...

Yellow Fever: The Jungle Story

For more than four centuries, right into the early twentieth century, coastal populations in Europe and in North, Central and South America suffered repeated outbreaks of a dreaded illness known variously as yellow jack, vomito negro, Barbados distemper, bilious fever, the American Plague or just yellow fever.¹ The origin of the disease, its specific cause, the mode of transmission: all were unknown; but its frequent recurrences and high fatality rate – as high as 50% in some summers – were well established. As soon as summer arrived, port cities in Europe as far north as Ireland, Central America and the Caribbean, and the United States as far north as Boston experienced recurrent, life-threatening outbreaks of yellow fever. The disease was first recognizably described in a Mayan manuscript in 1648 and designated formally as yellow fever (YF) in 1750, but for coastal dwellers from Spain to Northern Ireland, from the Caribbean to Boston, it was the scourge of summer.² Yellow fever was and remains an international problem, but unravelling the story of yellow fever is an American story ...

The Disease

Yellow fever can be recognized from historic texts stretching back hundreds of years because of its classical symptoms.³ The initial presentation is like many viral

illnesses, beginning with abrupt onset of fever, headache, chills, fatigue, muscle pain especially in the neck and back, nausea and loss of appetite. In addition, the yellow fever virus has a specific property called “viscerotropism” which reflects a predilection to preferentially infect the organs of the body, especially the liver, heart and kidneys. This is evident even at this early stage where subclinical findings of liver involvement appear as a rise in hepatic enzymes. The virus is also neurotropic – meaning attracted to the nervous system – but actual brain infection is extremely rare. In most infected individuals, disease symptoms resolve in 3–5 days but in 15–25%, there is a one- or two-day hiatus when symptoms improve before a second, toxic phase of the disease begins, characterized by recurrence of high fever, abdominal pain and jaundice (visible yellowing of the eyes and the skin), relative bradycardia (slow heart rate), low urine output and hematemesis (vomiting blood). These severe symptoms reflect the involvement of the liver, kidneys and heart. At this stage, liver enzymes are markedly elevated and liver function is affected, resulting in evidence of coagulopathy (clotting problems) with bleeding ranging from bruising to nosebleeds to severe hemorrhage. Multisystem involvement can occur with failure of the liver, kidneys and heart plus delirium, seizures and coma. Despite these last signs of central nervous system involvement, autopsies have not revealed infection or inflammation of the brain. After 5–10 days, this toxic progression is fatal in 20–50% of manifest cases giving an overall YF fatality rate of 3–8%. Older age, higher neutrophil (white cell) count, greater evidence of liver dysfunction (higher liver enzymes, bilirubin and clotting times), higher creatinine levels indicting kidney failure, and higher RNA plasma viral load all correlate significantly with a fatal outcome.⁴ Because the diagnosis of uncomplicated YF is not made in the majority of cases, the mortality rate based on manifest infection has often been overestimated. Even now, there is no specific treatment, but intensive supportive care can decrease mortality in patients with the severe form of the disease. In those who survive, recovery can be very prolonged, but there is usually no permanent organ damage.

Only after antibody studies became available was it realized that at least half of individuals infected with the yellow fever virus are completely asymptomatic and 35% have the mild form of the disease with complete recovery in only a few days. Only 15% of infected individuals develop the classic, severe form of the disease which is the historic yellow fever picture.⁵ The reasons for variation among patients infected with the same virus stem from a complex system of virus–host interactions, including intrinsic and acquired host resistance factors and differences in pathogenicity of different virus strains. Surviving the infection – whether asymptomatic, mild or severe – provides lifelong immunity.

Yellow fever was the first recognized viral hemorrhagic fever and is the prototype for this group of life-threatening diseases, represented most prominently at this time by Ebola. These pathogens combine multiple mechanisms to produce symptoms related to damage to the walls of small blood vessels and to the liver, interfering with the body’s ability to clot. The internal bleeding that results can range from relatively minor to life-threatening. Each hemorrhagic fever virus acts

on the body in pathogen-specific ways, resulting in a variety of symptoms in association with bleeding.

Yellow fever brought devastating morbidity and mortality from at least the 1500s right into the early twentieth century when major outbreaks in the port cities of Europe and North, South and Central America recurred. One exceptionally well-documented epidemic occurred in Philadelphia in the long, hot summer of 1793.^{6,7} At that time, Philadelphia was the nation's capital and the largest city in North America; trade with the Caribbean islands was common, primarily for sugar and coffee. In the first week of August, a ship from Santo Domingo was unloaded at the port. As vividly described by Murphy in *An American Plague: The True and Terrifying Story of the Yellow Fever Epidemic of 1793*, a young sailor from the ship fell violently ill with fever and died within a few days in a boarding house in the city.⁶ Within 2 weeks, there were seven more deaths on that same block, all associated with severe fever. By the third week of August, Philadelphia doctors were seeing many cases of this "bilious fever," clustered in the streets around the dock area. A massive exodus of panicked citizens began: ultimately, as many as 20,000 citizens of the total population of 55,000 are reported to have abandoned the city during the outbreak. The exodus included George Washington and his family, who moved temporarily to Germantown, MD. Doctors struggled to deal with the increasing numbers of desperately ill people. The famous physician Benjamin Rush lived in Philadelphia at the time, but even he had nothing to offer except the useless bleeding and purging that he had established as standard of care for almost every illness at that time.⁷ Between illness, death and departure, the city was increasingly deserted, but the epidemic raged on through September and into October. It was only after the weather turned decisively colder at the end of October that the epidemic ended. It is estimated that 5000 people, 10% of the population, died during the Philadelphia yellow fever epidemic of 1793.

This was the pattern of the long series of yellow fever outbreaks that descended on port cities – when summer came and ships from the Caribbean and Central America arrived, yellow fever emerged again and again.¹ At least 25 major epidemics were recorded in the United States alone with repeated summer outbreaks in Philadelphia, Baltimore and New York through the eighteenth and nineteenth centuries. In the American south, there were annual outbreaks with especially deadly epidemics described along the Gulf Coast in New Orleans in 1853 and in the whole lower Mississippi Valley in 1878 – 20,000 people died in that single epidemic. The last major outbreak in the United States occurred in 1905 in New Orleans. Europe was not spared with repeated epidemics – also in port cities – recorded as far north as Northern Ireland. It is no exaggeration to say that yellow fever was among the most dreaded diseases of that time.³

The Vector

By the nineteenth century it was recognized that yellow fever did not spread from person to person, but the true mode of infection and transmission was unknown. At

the time, the prevailing theory of disease causation was still the “miasma theory” – lethal disease-causing agents were thought to arise spontaneously from decomposing material in the earth and travel by air as a poisonous, foul-smelling vapor, leaving disease in its path. The often-observed association between hot weather and increasing stench with the outbreak of diseases like malaria and yellow fever certainly supported this theory. Another less widely accepted concept was that disease was transmitted by fomites which clung to the bedding and clothes of victims – this was closer to the idea of a contagious agent as the cause of disease proposed most clearly by Fracastero in 1546, but previously by others since ancient times.⁸ It was not until 1796 that John Crawford, an Irish-American physician, promoted a new concept of disease causation in a series of essays about malaria which directly contradicted the miasma theory. He thought that malaria was “occasioned by eggs ... laid during a mosquito bite, hatched in the wound and migrated through the host’s body” producing the manifestations of the disease.⁹ While rejected entirely by the scientific community, this was the first expression of an insect vector for disease. In 1850, Josiah Nott, an American physician living in Alabama, took up the idea that insects – including mosquitoes – were also the disease vector for yellow fever. Although a detailed exploration of his writings suggests that this was not a fully formulated idea, Nott is credited with the concept of mosquitoes as the agent for dissemination of yellow fever.^{10,11} The mosquito as vector of both yellow fever and malaria was clearly described by Dr. Louis-Daniel Beauperthuy, a physician from Guadalupe, in 1854 when he wrote that they are “produced by venomous fluid injected under the skin by mosquitoes, like poison injected by snakes.”¹² Then, in 1860, the French microbiologist, Louis Pasteur, determined that bacteria cause disease and Robert Koch subsequently defined the procedure for proving that specific diseases are caused by specific bacteria.¹³ Together, they formalized the germ theory of disease and transformed the concept of disease causation, with subsequent, significant impact on the understanding of yellow fever.

The yellow fever story then shifts to Havana, Cuba where repeated outbreaks of yellow fever occurred, beginning in 1620 after the arrival of a Spanish fleet from Panama. Two centuries later, phylogenetic studies using gene sequencing like those used to try to track the origin of the smallpox virus show that the yellow fever agent first appeared in East Africa approximately 3000 years ago and then spread to West Africa.¹⁴ Analysis of viral isolates from outbreaks in Africa and Central and South America, and an outbreak in the Canary Islands in 1494 have been used to develop the evolutionary history of yellow fever in the Americas.¹⁵ These studies demonstrate that the spread of yellow fever to North and South America corresponded closely with the timing and the routes of the slave trade, from West Africa to Central America and the Caribbean Islands.^{16,17} Once introduced, YF spread widely wherever mosquito populations supported it: from port cities in Central America and the Caribbean Islands, to North America as far as Massachusetts and South America along the coast of Brazil. In Cuba, a continuous yellow fever epidemic raged between 1649 and 1655, wiping out one third of the population. By the end of the nineteenth century, yellow fever had been continuously present in Havana for more than a hundred years.

In response to this ongoing epidemic and the recurrent outbreaks at home, especially a very severe epidemic in the Mississippi River valley in 1878, the United States National Health Board sent an official commission, the Havana Yellow Fever Commission, to Cuba to study yellow fever in 1879.¹⁸ The group worked cooperatively with a similar commission from Spain addressing the same problem and described the epidemiology of yellow fever but made no other major discoveries. Perhaps their greatest accomplishment was to engage a young Cuban physician in the study of yellow fever: Dr. Carlos Finlay was designated as the official Cuban liaison to both commissions. Always inquisitive, Dr. Finlay saw microscopic evidence that the disease attacked small blood vessels and raised the possibility of a vector. He became convinced that mosquitoes, an abundant and ubiquitous presence in Cuba at that time, might be that vector. From his writings:

It occurred to me that to inoculate yellow fever (into blood vessels) it would be necessary to pick out the infectious material from within the blood vessels of a yellow fever patient and to carry it likewise into the blood vessel of (another) person. All of which conditions the mosquito satisfied most admirably through its bite.¹⁹

Finlay then identified the *Culex cubensis* mosquito – now called *Aedes aegyptii* – as the most likely vector because of the two prevalent mosquito species in Havana at that time, it preferred to live in proximity to humans. He then tried to use *Culex* mosquitoes infected by biting yellow fever patients to infect military volunteers with a dramatic initial result: the very first subject developed classic symptoms of yellow fever 9 days after being bitten. Although subsequent findings were variable (very likely because infection is asymptomatic in more than half of people), Dr. Finlay presented the results of his investigations to the Academy of Sciences in Havana in 1881 in a report entitled, “The mosquito hypothetically considered as the agent of transmission of yellow fever.”²⁰ His audience was unimpressed but, undaunted, Finlay continued his work. By 1900, he had inoculated 102 volunteers using a single bite from an infected mosquito with mixed results in terms of classic yellow fever episodes but impressive long-term immunity in almost half of his subjects.

During the Spanish–American war (April to August, 1898), more American soldiers died from yellow fever and malaria than from combat. After the war, yellow fever continued to ravage both the Cubans and the Americans in Cuba as an occupying force. In response, the US military sent a new Yellow Fever Commission led by Major Walter Reed, accompanied by James Carroll, Jesse William Lazear and Aristides Agramonte.²¹ Unable to identify any other convincing cause, the Commission met with Carlos Finlay, who described his experiments and gave the group a sample of eggs from mosquitoes he believed were contaminated with yellow fever to initiate their investigations. Reed tested the mosquito theory by hatching the eggs from Finlay’s collection and then allowing them to bite several volunteers, including Lazear and Carroll from the commission team. Both Carroll

and Lazear developed yellow fever and Lazear died of the disease, providing tragic proof to Major Reed that mosquitoes transmitted yellow fever. After Lazear's death, the team developed a systematic series of experiments based on his notes which described critical timing issues in both the acquisition of the yellow fever agent by a mosquito and the mosquito's ability to transmit the infection.²² These experiments proved that mosquitoes can only acquire the yellow fever agent if they feed on an infected person during the first 3–5 days after they are infected and that mosquitoes cannot pass on the infection to another human until after a 10–12-day period of incubation. The team also conclusively eliminated the theory that yellow fever was transmitted by fomites: volunteers were isolated in separate buildings, one containing clothing and bed linens from yellow fever patients and the other containing infected mosquitoes. Only volunteers in the building containing mosquitoes developed yellow fever.²³ Finally, James Carroll, an expert in bacteriology, showed that yellow fever was caused by a filterable agent found in the blood of infected patients which caused yellow fever when injected into non-immune volunteers.²⁴ Remember that at that time, viruses were defined by two negative characteristics: they were not retained by standard bacteriologic filters and they were not visible by light microscopy. They could only be further identified indirectly by inducing disease in a susceptible host with a bacteria-free filtrate from a diseased subject, or by proven prevention of re-infection in survivors of the illness in question. Carroll's demonstration that a filterable agent in the blood of yellow fever victims induced the disease in non-immune volunteers was the very first demonstration that a virus could cause a specific disease in humans (Figure 3.1). The Fourth Yellow Fever Commission team definitively proved that the *Culex cubensis* mosquito – now *Aedes aegyptii* – was the mode of transmission for the yellow fever agent and that this agent was a virus. [This work is documented in remarkable detail in the *Philip S. Hench Walter Reed Yellow Fever Collection (circa 1800– circa 1998)*, located in “A Collection in Historical Collections” in the Claude Moore Health Sciences Library in the University of Virginia.]

As a result of the findings of the Reed Commission, Major William C. Gorgas, the Army's chief sanitation officer in Cuba, was ordered to implement a program of mosquito eradication. Gorgas first isolated yellow fever patients with screens to prevent mosquitoes from feeding on them and acquiring the virus. He then attacked the mosquito population, ordering his team to fumigate every building in Havana with insecticides and eliminate all sources of standing water. As a result of these efforts, the number of yellow fever cases fell precipitously and, by 1902, no new cases were reported in Havana. With Gorgas' practical application of the Reed Commission's findings, the Army was able to curb and (by the evidence of the time) eradicate yellow fever in Havana, paving the way for future operations in any environment where yellow fever was prevalent. Gorgas implemented a similar program during the building of the Panama Canal in 1905 after roughly 85% of workers in the initial attempt had been hospitalized with either malaria or yellow fever. He convinced President Theodore Roosevelt to fund a mosquito eradication effort in Panama and then led a team of 4000 workers, his “mosquito brigade.” The team

fumigated all the homes in the area and aggressively eliminated all standing water. Within a year, new cases of yellow fever had been virtually eliminated, a critical factor in completion of the Canal in 1914.²⁵ (For more on this fascinating story, see the history perspective at the end of this chapter.)

THE VECTOR



FIGURE 3.2 *Aedes aegyptii* mosquito.

Source: CDC.gov

As shown in Figure 3.2, the adult *Aedes aegypticus* mosquito is a supremely elegant insect, approximately 4–7 mm long. Dark brown to black in color, each has a silvery-white pattern on the top of the thorax in the shape of a harp and white basal stripes on each segment of the hind legs. With their long delicate wings, they are the divas of the mosquito world. In his comprehensive study of this mosquito, Sir Richard Christophers describes “blood as the natural food of the female,” while both males and females survive on nectar or sap from plants and flowers for nutrition.²⁶ The blood meal is essential for the development of eggs so females seek out a warm-blooded animal, usually a human, within a few days after breeding. The insect is so quiet and so light that its landing is usually entirely undetected. From close observation of feeding behavior, the female mosquito lands on exposed skin, shifts its proboscis into a nearly vertical position and quickly punctures the skin. The insect then crouches down, sinks the fascicle to its full depth and, if uninterrupted, feeds for up to 3 minutes until the abdomen is greatly distended before withdrawing the fascicle. More often, multiple bites on several different people are needed to take in enough blood. After feeding, flight is difficult because the weight of blood taken can actually exceed the weight of the unfed insect. The fully engorged

mosquito can remain sitting on the skin for as much as 15 minutes. The female then rests for a period of days during which digestion occurs followed by egg maturation. This can take 3 days to 3 weeks, depending on the temperature, with faster maturation at higher temperatures, before the eggs are laid on the surface of small collections of fresh water and the life cycle begins again. If the female mosquito bites an individual with yellow fever during the first 5 days of the illness, she acquires lifelong yellow fever infectivity. After approximately 10–12 days for virus incubation, an infected female will inoculate approximately 1000–100,000 virus particles with each subsequent bite. Female mosquitoes can lay a set of up to 100 eggs about every third night after mating only once. They typically lay as many as three sets before dying, requiring a blood meal to provide protein for each set.²⁶

A. aegypti is the perfect urban vector of yellow fever because it is rarely found more than 100 yards from human habitation. It is active in the daytime and early evening and prefers heavy shade. It freely enters homes and other buildings and has even been shown to readily move vertically in high rise buildings.²⁷ Within homes, the largest numbers are found in bedrooms, in secluded places like closets and under beds.²⁸ In short, humans are the perfect hosts, providing comfortable, safe shelter and plentiful food, all under one roof.

Although the mosquito is now widely established throughout the tropical and subtropical regions of the world, it was located solely in Africa until the fifteenth century.²⁹ At that time, *A. aegyptii* is thought to have adapted to breeding in small water collections in response to a profound drought. Such breeding sites were often man-made objects that contained water, from buckets to saucers to the water-storage jars on ships – thought to be the genesis of the described close connection between the mosquito and human habitation. This “human-adapted” behavior explains the mosquito’s spread across Africa and the introduction to the new world on slave trade ships between the fifteenth and eighteenth centuries. Slave ships carrying thousands of West Africans together with the domesticated *A. aegypti* mosquito allowed breeding and disease transmission cycles to be established en route.^{16,17} Arrival in Central America delivered a critical mass of viremic hosts and active vectors into a receptive environment. This allowed rapid dissemination of yellow fever across the tropical regions of Central and South America, where it caused the recurrent yellow fever epidemics of the next three centuries.

As described in the Philadelphia epidemic,⁶ the mosquitoes then travelled from their natural tropical habitat to temperate harbor cities in Europe and North America on trade ships carrying sugar and coffee. The ships had all the mosquito’s requirements: cisterns of water, humans in crowded conditions and concealed spaces. The recurrent yellow fever epidemics in port cities in the eighteenth and nineteenth centuries where the population was largely non-immune were the consequence of transportation of the *A. aegypti* mosquito in conjunction with human migration and trade.^{16,17}

With the dramatic successes of Reed and Gorgas, it was believed that the *Aedes aegypticus* mosquito was the sole vector responsible for transmission of yellow fever and that man was the only susceptible host. Mosquito eradication efforts carried out in many large Central and South American cities appeared to lead to the disappearance of yellow fever and at the time, scientists felt that mosquito eradication was all that was needed to completely eradicate the disease. This conviction was held so strongly that in 1915, the Rockefeller Foundation felt confident enough to pledge eradication of yellow fever from the face of the earth.³⁰ Unfortunately, sustained mosquito eradication efforts proved unsuccessful in eliminating YF in South America, suggesting the underlying epidemiology of the disease was more complicated.

Following reports that yellow fever was prevalent in West Africa, the West African Yellow Fever Commission was organized by the Rockefeller Foundation in 1925. Led by retired Colonel Henry Beeuwkes, the commission was charged with isolating the organism causing the disease, confirming the method of transmission and identifying those areas in which the disease is continually present. Attempting to establish an animal model, Beeuwkes imported monkeys and chimpanzees to the laboratory in West Africa which was already stocked with guinea pigs. Adrian Stokes, a pathologist with the Commission, injected blood from a West African man with yellow fever into the group of laboratory animals. Neither guinea pigs nor marmosets had any reaction, but a rhesus monkey became sick and died with autopsy findings consistent with yellow fever: an animal model was born.³¹ Unfortunately, Stokes himself developed yellow fever. Despite his illness, he insisted that his blood be injected into rhesus monkeys and that *A. aegyptii* mosquitoes be allowed to feed on him. Both his blood and the infected mosquitoes caused fatal yellow fever in the laboratory monkeys, thus fulfilling Koch's postulates for disease causality. Subsequent successful isolation of the virus and its confirmation as the cause of yellow fever came at a heavy price, as 32 laboratory-associated cases of the disease occurred between 1927 and 1931, with five deaths including that of Adrian Stokes. The isolated virus was named the *Asibi* strain after the 28-year-old West African yellow fever survivor who provided the blood sample.

Epidemiology of Yellow Fever

Continued work of the West African Yellow Fever Commission began to untangle the complex epidemiology of yellow fever. Once the virus had been isolated, a team from the Rockefeller Foundation headed by Max Theiler developed a test to demonstrate immunity to yellow fever when white mice were found to be susceptible to the virus. This "mouse protection test" could be used to test for the presence of antibodies to the virus and was utilized to conduct an immunity survey, testing serum collected from multiple sources.³² These results revealed a broad band of yellow fever immunity stretching across Africa, from the West Coast through Central Africa to Uganda in East Africa, from approximately 15° north to 15° south of the equator.³³ However, while clinical outbreaks of yellow fever were common

in West Africa, they were rare in East Africa. This led to the concept that yellow fever arose in East Africa and was potentially endemic there with such ubiquitous immunity that no yellow fever cases could develop. After intensive epidemiologic work, this concept was confirmed when multiple monkey species in the jungle forests of Uganda in East Africa were found to have immunity to yellow fever. In 1941, Alexander Mahaffy and his team from the Commission isolated the yellow fever virus from wild-caught *Aedes simpsoni* mosquitoes and from a human with clinical yellow fever during a local epidemic in Uganda in East Africa.^{33, 34} Multiple additional *Aedes* mosquito species found in the tropical forest canopy like *africanus* and *aldopictus* were also found to carry the virus. The YF virus was maintained in the jungle by transmission from female mosquitoes to their offspring and to lower primate vertebrate hosts, primarily monkeys. Outbreaks in humans in this situation occurred only with contact with the forest. In towns and cities, the virus was found to be primarily transmitted by the highly domesticated *A. aegypti* while in the forest, the virus was transmitted by several other jungle mosquito species. In all settings, the infected hosts – monkeys or humans – greatly increased the number of circulating viruses, a process called amplification. The virus was shown to be carried from one host to another by the biting mosquito vector, a horizontal transmission pattern. Mosquitoes also passed the virus via infected eggs to their offspring by vertical transmission. The eggs produced were resistant to drying, lying dormant through drought conditions and hatching when rain began. The mosquito was therefore recognized as the true reservoir of the virus, ensuring transmission from one host to another and from one year to the next.

These observations ultimately led to description of three separate yellow fever transmission cycles.³³ The *jungle* or *sylvatic cycle* of yellow fever involves endemic disease in tropical rain forests in para-equatorial Africa and South America where multiple *Aedes* tree-hole mosquito species that inhabit the forest canopy are the reservoir for the yellow fever virus. These mosquitoes transmit the virus to monkeys and other small mammals. There are only occasional human cases of yellow fever in this setting because contact between jungle mosquitoes and man is rare, but when the disease occurs, it is identical both clinically and serologically to classic urban yellow fever. The *intermediate* or *savannah cycle* occurs in areas with sparse human habitation bordering jungle areas, in Africa and South America. Multiple mosquito species which inhabit the jungle borders are involved in viral transmission including *Aedes furcifer*, *A. luteocephalus*, and *A. simpsoni*. It is these mosquitoes from the forest canopy that Allison and I encountered on our trip to Venezuela. Human cases of yellow fever occur in response to bites by these mosquitoes, but because contact with humans is infrequent, large outbreaks are rare and are usually associated with movement of groups of people into the area during periods of social unrest. The *urban cycle* is the already described classic form of the disease which occurred as recurrent epidemics in West Africa, Europe, Central, South and North America from the eighteenth into the twentieth centuries. In this setting, the yellow fever virus is transmitted from human to human by the *Aedes aegypti* mosquito. Because of the preference of this species for human habitation and human blood, the urban

pattern of transmission has the potential to cause explosive epidemics of disease when the virus is newly introduced into areas with high human population density.

The Vaccine

Discovery of the extent of endemic yellow fever in the jungle mosquitoes and monkeys of Africa and South America led to a clear understanding of why insect eradication in urban centers would not eliminate the disease so attempts at vaccine development began as early as the late 1920s. True isolation of the virus in 1928 was followed by several critical observations: demonstration that serum from humans and monkeys that had survived yellow fever protected monkeys against experimental yellow fever; a preliminary vaccine based on a killed virus did not confer immunity; and serum from disease survivors in South America protected against the YF virus in Africa.^{35,36} All these findings suggested that a live vaccine was needed and, if developed, would be globally protective against yellow fever.

In 1930, the Rockefeller Institute in New York was already the world's most important center of experimental yellow fever research. Conditions for experimenting with monkeys had been established and the basic properties of the virus had been analyzed. It was here that Max Theiler, who had already developed the mouse antibody test that demonstrated the presence of yellow fever antibodies in humans and was used to map the epidemiology of yellow fever in Africa, began work on a yellow fever vaccine.³² The Rockefeller team was familiar with the technique that Louis Pasteur developed to create the first laboratory-produced human vaccine for rabies in 1879, by creating a weakened or attenuated live virus. The attenuated form was created by passing the disease-causing virus through a series of cell cultures, animals or chick embryos. With each passage, the virus improved its ability to replicate in the new setting, but decreased its ability to replicate in human cells. A virus targeted for use in a vaccine may be "passaged" through as many as 200 different cultures before it will no longer multiply in humans. The goal is to create a weakened virus that will be unable to cause illness but will still provoke an immune response that will protect against future infection.³⁷

Initially, Theiler and his colleagues struggled to grow the yellow fever virus in tissue cultures. Eventually, based on Pasteur's work, they demonstrated growth in a mouse brain model.³⁸ After serial passage of the yellow fever virus through laboratory mice, Theiler found that this weakened virus conferred immunity in rhesus monkeys. Unfortunately, while the attenuated virus had diminished ability to attack the liver (its natural, viscerotropic property), the capacity of the virus to attack the brain – its latent neurotropic property – had increased.³⁹ To address this, Theiler and his team performed a series of experiments, passaging the virus multiple times in different kinds of tissue cultures and then repeatedly testing for neurotropic activity. A major breakthrough came in 1937 when the *Asibi* strain of virus – the first ever isolated – was passaged repeatedly in minced chicken embryos from which the central nervous system had been removed. After more than a hundred passages, a virus variant spontaneously emerged that lacked both the viscerotropic

and the neurotropic properties of the native virus – a very fortuitous example of spontaneous mutation. Fortunately, the properties of this new attenuated virus strain were stable, and virulence for the central nervous system did not recur on repeated testing. The Theiler team named this strain “17D.” Animal tests showed the attenuated 17D mutant was both safe and immunizing, allowing Theiler’s team to rapidly complete the development of a 17D vaccine.⁴⁰ For this work, Max Theiler received the Nobel Prize for Medicine and Physiology in 1951, the only Nobel ever given for development of a vaccine.

The new vaccine was not harmless – from the outset, there were severe neurological reactions in a very small number of people – but on balance, the 1937 field trials with the new 17D vaccine in Brazil, directed by the Rockefeller Foundation, were highly successful. Following these, the Foundation funded large-scale manufacture of the vaccine. During World War II, the Foundation coordinated the vaccination of all American and British military personnel. Some adverse reactions related to batch manufacture had to be addressed, but overall, this massive campaign was reportedly successful. By war’s end, millions of vaccine doses had been given with effective protection of active military personnel from yellow fever. Following the war, the manufacture and distribution of the yellow fever vaccine passed from the Rockefeller Foundation to the United States Public Health Service, as well as to other international institutions and government agencies.⁴¹

A second live-attenuated vaccine was developed almost concurrently with the Theiler vaccine from a YF virus strain isolated in Senegal, in 1937. This vaccine was widely and successfully used from the 1940s to the 1960s in French-speaking African countries, virtually eradicating the disease in these sites. However, because of high rates of post-vaccine encephalitis, the French neurotropic vaccine was abandoned in 1962.³¹

The question of safety of the 17D vaccine emerged again with the 2001 publication of a report of seven cases of acute multi-organ failure resembling classic, severe yellow fever occurring after vaccination; the infection was called YF vaccine-associated viscerotropic disease (YEL-AVD). Over the next decade, 65 similar cases of YEL-AVD were reported with a very high fatality rate of 63%. YEL-AVD ultimately proved to be extremely rare, occurring in 0.4 cases per 100,000 vaccinations, although the rate is higher in those over 60 years of age, 1.0–2.3 per 100,000. Extensive evaluation suggests that YEL-AVD occurs in individuals with an underlying, unrecognized immune defect.⁴² Another vaccine-associated reaction – yellow fever-associated neurotropic reaction (YEL-AND) – was reported beginning in the 1940s with either a meningitis/encephalitis picture attributed to viral central nervous system (CNS) injury or development of Guillain-Barré syndrome, as seen in reaction to other acute viremias. YEL-AND is also rare, reported at 0.8 per 100,000 vaccinations, and almost all patients recover completely.⁴² With knowledge of these rare but serious reactions, the YF vaccine is still widely in use, contra-indicated only in individuals with immune suppression and in babies less than 9 months of age; in individuals over 60 years of age, the vaccine is given electively, with agreement of the clinician and patient.

The Virus

Against the backdrop of ongoing vaccination programs, characterization of the yellow fever virus itself continued, albeit at a leisurely pace.⁴³ In 1953, the virus was first visualized by electron microscopy and was seen to be small and round with a slightly irregular contour as demonstrated in Figure 3.1.⁴⁴ By the 1960s, antibodies against yellow fever could be identified by simplified laboratory tests, and these results led to the realization that the YF virus was antigenically related to a group of viruses called the Arboviruses because they were all carried by arthropods – mosquitoes or ticks. This terminology was formally adopted by the WHO in 1963.⁴⁵ The yellow fever virus is a single-stranded positive-sense RNA virus. Ultimately, reverse transcription-polymerase chain reaction (RT-PCR), the genetic test that identifies nucleotide sequences, was applied to the yellow fever virus and complete sequencing of the virus was first reported in 1985.⁴⁶ Based on this nucleotide sequencing, a new taxonomic classification, the *Flavivirus* genus, was created in 1994. The first mammalian viruses to be assigned to this classification included the yellow fever virus which lent its Latin name, “flavus,” for the characteristic yellow color of its victims, to the group. The yellow fever virus is the prototype member of the *Flavivirus* genus which includes more than 70 taxonomically recognized, globally distributed species and is constantly being updated to reflect newly identified viruses and advances in analytical methods.⁴⁷

The family Flaviviridae contains three genera: the above-described flaviviruses, which include yellow fever virus (YFV), West Nile virus (WNV), dengue virus (DENV) and Zika virus (ZIKV); the hepaci-viruses, which include hepatitis B and C viruses; and the pesti-viruses, which infect hoofed mammals. The vector-borne arboviruses are grouped as a clade within the *Flavivirus* genus and this is subdivided into a mosquito-borne clade and a tick-borne clade. The mosquito clade is divided into two branches: one branch contains the neurotropic viruses, often associated with encephalitic disease in humans or livestock. This branch tends to be spread by the *Culex* mosquito species and to have bird reservoirs – an example is the West Nile virus. The second branch is the group associated with hemorrhagic disease in humans. These tend to have *Aedes* species as vectors and primate hosts – the yellow fever virus is emblematic of this group.⁴⁶

The yellow fever virus is now known to be a small (40–60 nm), enveloped virus harboring a single positive-strand RNA genome of 11 kb that like the smallpox virus, replicates in the cytoplasm of infected cells. The genome encodes a polyprotein that is cleaved into three structural proteins and seven non-structural proteins. Surface macromolecules of the YF virus are its main virulence factors and contribute to the entry, signaling and cell–cell interactions of the virus. During virus replication, the structural proteins are incorporated into progeny virions, while the non-structural proteins remain in infected cells where they coordinate RNA replication and viral assembly, and modulate innate immune responses.⁴⁶ The synthesis of yellow fever virus RNA is detectable within 3–6 hours after infection and progeny virions created in the host cell are released after about 12 hours.

Patterns of antigenic conservation and divergence differ widely between different viruses: the yellow fever virus is a single antigenic serotype which is highly conserved and this is why the 17D vaccine protects against all strains of the virus. At the nucleotide sequence level, it is possible to distinguish seven major genotypes of yellow fever representing West Africa (two genotypes), Central–East Africa and Angola (three genotypes), and South America (two genotypes). Unlike the influenza virus, spontaneous mutation is not a common feature of the yellow fever virus.⁴⁷

Laboratory confirmation of YF is required for diagnosis but is rarely accomplished because the majority of infected individuals are asymptomatic and testing requires highly trained laboratory staff and specialized equipment and materials. Laboratory criteria for diagnosis are any one of the following: (1) the presence of YFV-specific IgM antibodies or a fourfold or greater increase in IgG antibody levels between acute and convalescent sera; (2) isolation of the YFV; (3) positive postmortem liver histopathology; (4) detection of YFV antigen in tissues by immuno-histochemistry; or (5) most frequently, detection of YFV genomic sequences in blood or organs by PCR. Frequently clinical YF is not diagnosed until the patient has either recovered or succumbed, if a confirmed diagnosis is ever made. Case definitions state that a *suspected* case is characterized by acute onset of fever followed by jaundice within 2 weeks of the onset of the first symptoms, while a *confirmed* YF case requires laboratory confirmation or an epidemiologic link to a laboratory-confirmed case or outbreak.⁴⁸

Several studies investigating the immune response in healthy subjects receiving the vaccine have shown that 17D vaccination leads to an integrated immune response that includes several effector arms of the innate immune response as well as rapid activation of T-cell immunity and production of neutralizing antibodies within 10 days of vaccination; antibodies have been confirmed as persisting for up to 40 years.⁴⁹ Practically speaking, immunity after vaccination is believed to be lifelong.

The fascinating and beautiful *Aedes aegypti* mosquito has been shown to play a critical role in disease transmission for multiple members of the Flaviviridae family. It is the primary vector for yellow fever, but also one of the main transmitters of dengue, chikungunya and Zika, all increasingly important global public health concerns. Dengue alone is responsible for 50–100 million annual infections including major outbreaks in the southern United States. Since 2013, chikungunya virus has caused large disease outbreaks in India, Southeast Asia, the Caribbean islands, Latin America, South America and the southern United States. Finally, beginning in 2015, the Zika virus (ZIKV) – described in depth in Chapter 7 – has caused a major pandemic affecting more than 15 million people. Centered in Brazil, ZIKV infection in most patients causes no symptoms but in pregnant women in the first and second trimesters, ZIKV infection is

associated with significant risk for severe congenital brain abnormalities in the developing fetus. In summary, the easy co-existence of humans and *A. aegyptii* has major health consequences. The struggle to control *A. aegyptii* is reflected in the ongoing global struggle with all these diseases.

Public Health Management of Yellow Fever

Between the 1930s and the 1960s, mass YF vaccination campaigns were carried out in South America and in West African countries including Benin, Burkina Faso, Cameroon, Chad, Cote d'Ivoire, Congo, Gabon, Guinea, Senegal and Togo, resulting in a progressive disappearance of the disease in those locations. However, the range of yellow fever virus transmission in the Americas expanded with cases reported in Panama in the 1950s, the first in 43 years. Before the end of the decade, the disease had spread throughout Central America, finally stopping near the southern border of Mexico. From the 1960s forward, low or absent vaccination levels globally, combined with the births of subsequently unvaccinated children and the deaths of older, protected individuals resulted in increasing yellow fever outbreaks in Africa and in Central and South America. Thousands of cases were reported annually in West Africa, where vaccination coverage had waned or was absent, and in Ethiopia where the disease had never been reported previously.⁴⁷

Since the 1940s, the International Sanitary Regulations drafted by WHO have stipulated that “vaccination against yellow fever shall be required of any person leaving an infected local area on an international voyage and proceeding to a yellow fever receptive area.” This was the first regulatory language that overtly mandated yellow fever vaccination requirements for country entry. These were modified and renamed the International Health Regulations in 1969 and then completely revised in 2005; the most current iteration stipulates, “Vaccination against yellow fever may be required of any traveler leaving an area where the Organization has determined that a risk of yellow fever transmission is present.”⁵⁰ The WHO also asked countries to establish entry regulations, requiring travelers to show official proof of vaccination against the disease. Despite these regulatory efforts, vaccination programs anywhere in Africa between 1960 and 1980 were almost exclusively in reaction to disease outbreaks.

Since the 1980s, there has been an exponential increase in yellow fever cases in both sub-Saharan Africa and tropical South America. Between 1987 and 1991, a total of 18,735 yellow fever cases and 4522 deaths were reported to the World Health Organization – this was the highest level of yellow fever activity for any 5-year period since 1948; given the very high prevalence of clinically asymptomatic infection, the true number of cases will have been vastly greater.^{43,47} Ecological surveillance of jungle mosquitoes and monkeys suggested that these outbreaks occurred because of an amplification of the disease in nonhuman primates combined with an increasing population of unvaccinated individuals in progressively closer proximity – in other words, the progressive impact of human encroachment on

previously remote jungle areas.⁴³ Globally, WHO now estimates there are between 84,000 and 170,000 cases and 60,000 deaths from yellow fever each year; as always, there is significant under-reporting due to asymptomatic infections and lack of effective surveillance systems, so the actual disease burden is much higher. Yellow fever is an annual risk to 900 million(!) individuals and travelers in the 44 known endemic countries of Africa and Latin America, with West Africa as the region most affected; a large proportion of cases occur in children. Since 1988, the WHO, the United Nations Children's Fund (UNICEF), and the World Bank have recommended that 33 African countries add the vaccine to the routine immunization program in infants and children after studies showed that this would be highly cost-effective.^{51,52} In 2001, the Global Alliance for Vaccines (GAVI) began to fund a program to include the yellow fever vaccine in routine immunization programs and analyses show that 22 of the 33 countries had adopted the program by 2006. Immunizing children, however, will not prevent disease outbreaks when the rest of the population remains vulnerable. In response, the Yellow Fever Initiative was launched in 2005 as a partnership among WHO, GAVI, UNICEF, and the ministries of health in each country to begin a catch-up immunization campaign across West Africa and to secure a large, stable vaccine supply. By 2012, 69 million people in 13 countries had received the yellow fever vaccine.⁵³

Unfortunately, the demand for the yellow fever vaccine for preventive campaigns consistently exceeds availability. The limited global production capacity cannot meet the demand because routine immunization programs, preventive mass vaccination campaigns, and emergency response stockpiling are all on the increase. In addition, the manufacturing process for the yellow fever vaccine is slow and cumbersome, essentially unchanged from Theiler's method back in the 1930s, using 7–9-day-old chick embryos in specific pathogen-free eggs which are infected with the virus and then incubated for 3–4 days. The infected embryos are then harvested under aseptic conditions after which homogenization and centrifugation produces a surface liquid that is preserved for use in vaccines. Each embryo can produce only 100–300 vaccine doses and the supply of pathogen-free eggs is limited, making it difficult to rapidly increase vaccine production.⁵⁴ The emergency vaccine stockpile, administered by a WHO committee in Geneva, holds only six million doses. Because profits are low, many pharmaceutical companies have dropped production of the yellow fever vaccine. In 1970, 14 private or national vaccine factories made yellow fever vaccine; now only six do, and only four sell the vaccine to the World Health Organization.

In December of 2015, a new sustained yellow fever epidemic began in Angola and spread to the Democratic Republic of the Congo (DRC) with almost 1000 confirmed cases and 7300 suspected cases in those two countries by the fall of 2016.⁵⁵ With an at-risk population in Africa alone of over 500 million people, there was immediate concern about a massive epidemic with the potential for global spread. Ultimately, this outbreak developed into the largest and most widespread epidemic of YF in more than 20 years. The crisis initiated an emergency mass immunization campaign aimed to end disease transmission before the rainy

season started in September 2016, a peak time for yellow fever-carrying mosquitoes. The logistical details were daunting, requiring almost 20 million syringes and over 40,000 health workers and volunteers. The vaccine requires refrigeration and an unreliable energy supply made this a major challenge, with ultimately more than 100,000 ice packs used to deliver the vaccine.

The vaccines used came from the global stockpile co-managed by Médecins Sans Frontières (MSF), the International Federation of the Red Cross and Red Crescent Societies (IFRC), UNICEF and the WHO. In the first 6 months of 2016 alone, these partners delivered more than 19 million doses of the vaccine – more than three times the six million doses usually put aside for a possible outbreak. GAVI financed a significant proportion of the vaccines. Because the vaccine supply was so limited, WHO used a fractional dose strategy based on studies showing that one fifth of the usual dose of the yellow fever vaccine will provide immunity for at least a year – enough time to achieve the critical level of resistance needed to stop the outbreak.⁵⁶ A massive training and community engagement effort resulted in 30 million people being vaccinated across the two countries. The campaign was at least temporarily successful with no reports of suspected cases in Angola or the DRC after September 2016.⁵⁷

Experts state that outbreaks like those in Angola and the DRC could become more frequent in many parts of the world unless coordinated measures are taken to protect people most at risk. Recent years have seen global changes in the epidemiology of yellow fever, with outbreaks occurring in areas that were not previously assessed as being at high risk. Climate change, increasing population density, the mobility of people within and across borders, and the resurgence of the *Aedes aegypti* mosquito, have combined to increase the likelihood of yellow fever epidemics. Awareness of this increased global risk brought together a broad coalition of partners in Geneva, Switzerland, in September 2016 to develop a new global strategy for the “Elimination of Yellow Fever Epidemics” (EYE). Planned key components of the strategy include preventive vaccination (both in routine immunization schedules and mass campaigns), an expanded global vaccine stockpile for outbreak response and support for greater preparedness in the most at-risk countries.⁵⁸

Increasing global connectedness plays a major part in the expansion of *A. aegypti* territory: exponential growth in population density and urbanization and international trade and travel plus global warming each contribute to the increasing distribution of this mosquito. Incorporating climate and environmental data with land-cover variables and occurrence records in a complex model predicts the current distribution of this mosquito to be concentrated in tropical and subtropical areas across the globe, especially sub-Saharan Africa, northern Brazil and South-East Asia, northern Australia, Spain and Greece. The model predicts *A. aegypti* will be distributed throughout Central America and on both coasts of Mexico; in the United States, it will be concentrated in the south-eastern states, especially those along the Gulf Coast. As shown in Figure 3.3, this predicted distribution includes all five non-polar continents.⁵⁹



FIGURE 3.3 Global map of the predicted distribution of *A. aegypti*.

Source: From Kraemer MUG, Sinka ME, Duda KA et al. The global distribution of the arbovirus vectors *Aedes aegypti* and *Ae. aldopictus*. eLIFE 2015; 4: e08347. American Public Health Service. APHC.gov

Cases of yellow fever imported from countries with endemic and/or epidemic disease are an important factor in the potential for future epidemics. As an example, on September 28, 1999, a previously healthy 48-year-old Californian man presented to a local ER with a 2-day history of fever, chills, headache, photophobia, muscle and joint pain, nausea, vomiting and generalized weakness. Two days earlier, he had returned from a 10-day trip to Venezuela. His physical exam was positive for icteric sclerae (yellowing of the whites of the eyes), tenderness in the upper abdomen and multiple, red, excoriated mosquito bites on the lower legs and feet. His liver enzymes and liver function tests were all markedly elevated and he had biochemical evidence of acute kidney failure – all significant risk factors for a fatal outcome. Despite intensive management, his condition deteriorated rapidly with evidence of a severe clotting disorder and heart arrhythmias. He died 6 days after presentation. Autopsy findings confirmed the clinical diagnosis of fulminant yellow fever.⁶⁰ This was only the second case of yellow fever imported from South America in the United States since 1924; the other case occurred in 1997 in an American tourist who visited the jungles of Brazil along the Rio Negro and Amazon Rivers. These were both vaccine-preventable deaths as proof of yellow fever vaccination was required for travel to both countries by 1990, only a few years after Allison and I experienced our mass mosquito attack. At present, a high proportion of travelers to at-risk areas are reported to be immunized, presumably reflecting widespread knowledge about the International Health Regulations. However, with *Aedes aegypti* mosquitoes present in new areas including the coastal United States, there is concern that the yellow fever virus imported by unvaccinated travelers like these could erupt into explosive outbreaks in *A. aegypti*-infested areas now free of the disease.⁶¹

The 2015–16 epidemic in Angola is a case in point. Angola is one of China's biggest energy investment targets; in 2009, China bought almost one-third of Angola's crude oil. There are reportedly 100,000 Chinese construction workers and business people in Angola and an untold number in the DRC. In early March 2016, three months into the epidemic described above, a previously healthy Chinese man who had worked in Angola since 2009 developed fever and chills. He flew home to Beijing, arriving on day 3 of his illness, and was immediately admitted to hospital. Despite intensive efforts, he died on day 9 in fulminant liver and kidney failure. Yellow fever virus was detected in his serum and viral gene sequencing showed the infecting virus belonged to the Angolan subtype.⁶² After this case, the Chinese government notified the WHO of 11 additional cases of yellow fever imported from Angola. Despite Chinese, Angolan and WHO–IHR regulations, none of these individuals had received vaccination against yellow fever in China before going to Angola, nor in Angola before returning to China.

These are the first cases of yellow fever ever documented in China. One of the mysteries of yellow fever epidemiology has been its failure to emerge as an established pathogen in Asia despite appropriate tropical and subtropical environmental conditions, a susceptible urban population and the established presence of the *A. aegypti* vector. In addition, the dengue virus, also transmitted by *A. aegypti*,

is now an established disease in China. There are a number of theories to explain this phenomenon, including the possibility that Asian strains of *A. aegypti* may be less competent yellow fever vectors; limited introduction of a sustained volume of infected men or mosquitoes; and potential cross-protective immunity in individuals infected with other flaviviruses like dengue.⁶³ By contrast, there are contemporary factors that represent optimal conditions for an Asian epidemic. The volume of travelers entering the region on commercial airlines is very high: the Asian–Pacific region was the largest regional market for air transport in 2016, accounting for one-third of all global passengers. This allows for easy introduction of a large number of individuals carrying the virus into a country with the known mosquito vectors, as well as the potential for rapid dissemination to other high-risk regions in India or South-East Asia. Most importantly, there appears to be low effective vaccination coverage of Chinese workers in Angola. The risk of illness for an unimmunized person spending 2 weeks in an area of epidemic activity is high, estimated at 1 in 267. This translates into a substantial number of potential cases among returning workers, with the potential of sustained regional YF exposure. Finally, there is a strong possibility that widespread epidemic transmission could occur in Asia before it is recognized, given the similarity of the early clinical presentation to that of other endemic diseases and the lack of clinical experience with YF.⁶³ Fortunately, the infected Chinese workers who returned from Angola in 2016 all arrived in locations where *A. aegyptii* is not established and no secondary cases resulted.⁶⁴ The current scenario of a YF outbreak in Angola, where there is a large community of non-immune foreign nationals, coupled with high volumes of air travel to an environment conducive to transmission in Asia, is unprecedented in history. These conditions raise the alarming possibility of a YF epidemic in a region with a susceptible population of two billion(!) people and a limited infrastructure for effective response. Imported cases like these show how critical it is to recognize this risk now and initiate adequate pre-emptive action to avert a global catastrophe.

Yellow fever is also endo-epidemic in Brazil with seasonal increases in human cases occurring annually in coastal areas between December and May, but since 2016, massive outbreaks have taken place in Brazil, reaching YF-free zones and causing thousands of deaths. The 2016–2019 YF epidemics have been the most significant outbreaks of the last 70 years and the number of human cases was 2.8 times higher than total cases in the previous 36 years.⁶⁵ A new YFV lineage was associated with the recent outbreaks, with persistent circulation in south-east Brazil until 2019. As described, the typical jungle transmission cycle occurs between forest mosquitoes and forest-dwelling nonhuman primates, with humans serving only as incidental hosts. However, deforestation, which has reduced monkey habitats, combined with expanding urban sprawl have brought yellow fever-carrying primates and mosquitoes closer to human populations in this part of Brazil. In early 2016, the yellow fever virus broke out of its usual jungle transmission pattern; instead, the virus began moving south and east, following forest corridors inhabited by monkeys toward the big coastal cities with huge populations of non-vaccinated, YF-naïve individuals, triggering a potential public health emergency.⁶⁶ In previous seasons,

human YF cases were rare, but from 2016 through 2018, there were 2154 cases with 745 deaths. All cases have been related to sylvatic transmission by *Haemagogus* mosquitoes, a jungle species, but there is significant concern that a person infected with yellow fever in the jungle could easily travel to an urban area and be bitten by an *Aedes aegypti* mosquito, initiating an urban chain of human infections.⁶⁶ Yellow fever can spread explosively among unvaccinated people in this situation and international travel means many areas of the world where *A. aegyptii* are ubiquitous are at risk. As the epizootic waves of the 1916–1919 seasons drifted closer and closer to the large cities in the states of Sao Paulo, Rio de Janeiro and Bahia, the risk of urbanization of the virus led to a mass vaccination campaign. Initiated in January 2018, this ongoing campaign is utilizing the fractional dose strategy and as of the World Health Organization's report in April 2019, vaccination coverage has increased to an average of 55% across all three states. To the time of this writing, no YF cases secondary to transmission by *A. aegyptii* – signaling urban transmission – have been reported.⁵⁵

New YF cases were reported again in Uganda in November 2019. Uganda is classified as a high-risk country in the EYE initiative, with a history of recurrent outbreaks in 2011, 2016 and 2018. The YF virus is endo-epidemic in Uganda meaning repeated disease outbreaks can be anticipated. Risk of epidemic spread is high because the estimated overall population immunity is very low. The affected districts in Uganda share international borders with DRC and South Sudan, both countries with enormous, unvaccinated populations that are marked by frequent population movements and high interconnectivity. There is significant risk of international spread with low population immunity in the cross-border areas and the continuous forest biome between countries. By the end of January 2020, more cases of YF had appeared and this was designated as a YF outbreak. Plans are once again underway for a mass vaccination campaign and for inclusion of YF vaccination in the routine immunization program.

In response to recurrent and increasingly large ongoing epidemics on two continents, the WHO recommends the traditional triad of surveillance, vaccination, and vector control. However, the global emergency YF vaccine stockpile is depleted, with not enough vaccine to even cover Angola's population during that recent epidemic. The production of new vaccine using the current method of embryonated chicken eggs is slow and limits the capability to rapidly produce large vaccine quantities in response to an outbreak. It is therefore highly unlikely that sufficient YF doses would be available for an effective emergency YF outbreak response anywhere in the world. Any vaccination program must be coupled with the development of systems that can support a rapid outbreak response. These include strengthening laboratory capacity, the ability to carry out epidemiological and entomological investigations, and emergency measures to interrupt transmission. Vector control will require destruction of urban mosquito breeding sites and public education about mosquito avoidance and elimination of domestic breeding sites. Clearly, new options are also required to address the threat of yellow fever

infection in non-immunized travelers returning from a country with endemic or epidemic disease.

Looking Back :: Moving Forward

The yellow fever virus was the first disease-specific pathogen identified as a virus. The story of this discovery, the recognition of the *A. aegypti* mosquito as the virus vector, the first epidemiologic description of the origin of the disease in East Africa and its transport to Europe and the Americas, recognition of the epidemiology of the disease, identification of the clinical pattern and the development of an effective vaccine conveying lifelong immunity are all dramatic successes. However, despite this early progress – most importantly, the existence of an effective vaccine since 1937 – large yellow fever outbreaks remain omnipresent in sub-Saharan Africa and in tropical South America, promoted by increasing global connectedness – specifically, increasing population density and urbanization, human encroachment on jungle habitats due to deforestation and urban sprawl, and climate changes including prolonged increases in rainfall and sustained higher temperatures enhancing spread of the *A. aegypti* vector. The stage is set for introduction of the yellow fever virus into *A. aegypti*-infested but YF-naïve areas resulting in a potential global YF pandemic.

Through his blog, Bill Gates, the Microsoft inventor and international philanthropist, has designated one week a year as “Mosquito Week,” trying to raise consciousness about the critical role the mosquito plays in global disease transmission. On his October 2016 blog he asks,

What would you say is the most dangerous animal on Earth? Sharks? Snakes? Humans? Of course, the answer depends on how you define dangerous. Personally, I’ve had a thing about sharks since the first time I saw “Jaws.” But if you’re judging by how many people are killed by an animal every year, then the answer isn’t any of the above. *It’s mosquitoes.*

He includes a stunning graphic, displaying the number of people killed by different animals in 2015: “The shark only gets credit for 6 worldwide deaths, while the mosquito notches an impressive 830,000.”⁶⁷ Gates has been involved in attempts to eradicate malaria – also transmitted by mosquitoes – for more than two decades. He is especially impressed with a new molecular biology technology called a gene drive. Using CRISPR–Cas9 DNA-editing technology, scientists have created genes that aggressively integrate themselves into a subject’s genome so that all offspring will inherit that gene. If, as some researchers have tried, the gene is one that keeps female mosquitoes from reproducing, the mosquito species in question will become extinct. The gene change cannot spread to other species of mosquitoes, so advocates say that it will not endanger the environment, or harm people.⁶⁷

To address the limited vaccine supply and questions about vaccine safety, new options for yellow fever vaccine are in development. In July 2016, the National Institute of Allergy and Infectious Diseases (NIAID), part of the US National Institutes of Health, announced initiation of a Phase I placebo-controlled, double-blinded clinical trial to evaluate whether an experimental vaccine developed by a Danish biopharmaceutical company is safe, tolerable and has the potential to prevent yellow fever virus infection.⁶⁸ The experimental vaccine, called MVA-BN-YF, uses an attenuated version of the Modified Vaccinia Ankara (MVA) virus as a vector to carry yellow fever virus genes into the body. More than 7600 people, including 1000 individuals who are immunocompromised, are reported to have been safely vaccinated with other MVA-BN-based vaccines. Previous studies have suggested that combining MVA-BN with an experimental immune-boosting adjuvant induces a strong immune response after a single dose of vaccine. One goal of this study will be to assess whether two doses of vaccine without adjuvant or a single dose of adjuvant-boosted vaccine will provide better protection. A separate company is taking a different approach, developing an inactivated or killed virus vaccine which would theoretically be safer than the current live attenuated version. Unlike the current vaccine which is produced in specially prepared, pathogen-free chicken embryos, this simpler process would rely on cell culture of a continuous cell line for production of yellow fever vaccine.

The other major component of yellow fever control is the management of mosquitoes which currently relies on either insecticides or the destruction of larval breeding sites. Widespread insecticide resistance and the impracticality of eliminating standing pools of water on a global scale have made this approach ineffective. Two novel approaches that have shown considerable promise in recent years are the genetic control of *A. aegypti* mosquitoes and the development of mosquitoes that are resistant to arbovirus infection. The first field-trialed genetic control strategy is known as RIDL (the Release of Insects carrying Dominant Lethal genes) and involves rearing *A. aegypti* that have been genetically modified to express a repressible lethal gene. During their rearing in insectaries, the mosquitoes are provided with a dietary supplement not present in nature that represses the lethal gene activation. Only male mosquitoes are released and these compete with wild males to mate with wild females. Offspring do not survive to the adult stage because they do not receive the dietary additive in the wild.⁶⁹ Lines of RIDL males have been shown to be competitive with wild males and a recent field release in Bahia, Brazil, reportedly achieved a 95% reduction in local mosquito populations.⁷⁰

An alternative approach is the use of endosymbiotic bacteria to prevent arbovirus replication in the mosquito. The “Eliminate Dengue Project” has demonstrated that infection of the dengue virus (DENV) with *Wolbachia* bacteria prevents transmission of the virus to *A. aegypti* mosquitoes.⁷¹ While developed to address dengue, *Wolbachia* also inhibits the replication of the viruses that cause yellow fever and chikungunya. *Wolbachia*-infected *A. aegypti* mosquitoes have been released in Australia and have been shown to successfully invade wild populations and stop dengue transmission at the community level.^{72,73} This approach would be equally effective

in reducing yellow fever transmission. Releases are ongoing in DENV-endemic countries such as Indonesia, Vietnam, and – a major site for recurrent yellow fever outbreaks – Brazil. What effect either RIDL or *Wolbachia* will have on arboviral transmission in the wild is unknown. Mathematical models predict that one strain of *Wolbachia* could reduce the basic reproduction number of DENV transmission by 70%. Models of DENV transmission control with RIDL also project high efficacy in reducing disease burden. These projections suggest that such strategies could have a direct impact on transmission of other arboviruses such as the yellow fever virus where *A. aegypti* is the principle vector. An important potential benefit of these species-specific approaches is that they are environmentally friendly, reducing dependence on insecticides. In addition, suppressing the mosquito population, or making it arbovirus-resistant, holds great potential for simultaneous control of multiple viruses.

It is likely that RIDL, *Wolbachia* or CRISPR-Cas9 gene-editing will eventually prove conclusively effective and become widely available – they may even be the YF answer the world is looking for. But to this time, the mosquito still prevails. Despite all that we have learned about the antigenically stable yellow fever virus, despite development of a highly effective vaccine that conveys lifelong immunity with a single shot and ongoing mass vaccination efforts, human-aided forces sustain global spread of the yellow fever virus carried by the *Aedes aegyptii* mosquito. Increasing global connectedness plays a major role: our exponentially increasing population brings humans and jungle breeding sites for sylvan transmission closer every year; deforestation concentrates the areas where both the virus and the mosquito vector can survive, closer to sites of human habitation; increasing urbanization creates ever larger, crowded habitats for *A. Aegyptii* to thrive; exponentially increasing worldwide air travel transports human virus carriers to enormous naïve populations where the mosquito vector already thrives. Global warming also increases the areas where *A. aegyptii* can breed and multiply. And failure to aggressively deliver effective human vaccination campaigns and establish emergency outbreak infrastructure in vulnerable areas sustains the cycle of disease transmission from mosquitoes to humans and humans to mosquitoes. From the fifteenth century right up to the present, the vector mosquito *A. aegypti*, well-adapted to humans and our habits, has caused explosive outbreaks of yellow fever. Introduction of the yellow fever virus from Angola into China exemplifies the ongoing threat of these fragile but deadly disease carriers. And as described, in November 2019, Uganda reported a new and ongoing northern and central outbreak initiating another reactive YF vaccination campaign. Yellow fever has become endo-epidemic in that country, confirming perpetual risk of another explosive epidemic.

HISTORIC PERSPECTIVE: YELLOW FEVER AS AN AGENT OF COLONIALISM

The story of yellow fever intersects in important ways with the history of globalization and, particularly, public health as an agent of colonialism.

It is likely that without the globalization of trade and the drive to find more efficient means of transporting goods around the world, yellow fever would have remained an obscure tropical disease. It is certainly true that the means of controlling yellow fever would not have been achieved so rapidly without the efforts of physicians, researchers, and public health experts from all over the world. It is a story that features the emergence of a new nation, marks a sharp loss for one of the great colonial powers and a big opportunity for an emerging power, and demonstrates the ways in which medical knowledge and public health strategies were to become important currencies on the larger and increasingly complex world stage. This section concentrates on these themes as a means of providing historical context for yellow fever and better understanding the influence it commanded in the early twentieth century.

The Panama Canal is a tremendous feat of engineering that took 33 years to complete but was part of the global imagination for three preceding centuries. The goal was to create an artificial waterway across the Isthmus of Panama to connect the Atlantic and Pacific Oceans and cut both the time and the risk for ships forced to circumnavigate the Straits of Magellan or Cape Horn. The idea of a canal began circulating as early as the 1530s and multiple proposals were made before the end of the nineteenth century. While Panama was not the only place where a canal was considered, its geography made it a logical solution to the problem. Charles V, the King of Spain and Holy Roman Emperor, was the first to propose a canal be cut there to ease the route of ships traveling from Spain to Peru. His primary concern was gaining a trading edge over Spain's great rival in colonialism and trade, Portugal. He ordered a survey of the area, but no construction was undertaken. In 1668 the English physicians and natural philosopher Thomas Browne noted the advantage to be gained by the country with the means and zeal to undertake building a canal where nature had failed to conveniently place a river. He speculated that it would be an ideal site for a man-made water lane connecting the oceans, which would open up trade for his own native country, an emerging imperial power, to access the rich trade in the East: "some Isthmus have been eat through by the Sea, and others cut by the spade: And if policy would permit, that of Panama in America were most worthy the attempt: it being but few miles over, and would open a shorter cut unto the East Indies and China."⁷⁵ Thomas Jefferson sided with the Spanish and proposed, in 1788, that they invest in it to expand their hold over trade in the Americas, and several years later, Spanish naval officer Alejandro Malaspina investigated the possibility, along with looking for the Northwest Passage, during his trip around the world to gather scientific specimens and further geographic knowledge (1789–1794). Nothing further came of it, as he was arrested for treason relatively soon after his return to Spain and imprisoned for 6 years, then banned

from the country. In 1843, the British took an active interest in building the canal and entered into a contract with the republic of New Granada to build it. Plans were drafted and a construction calendar established, but nothing came of that effort either, nor of another proposal to build a similar canal in Mexico.

The United States formally entered the race in 1846, when it signed the Mallarino–Bidlack Treaty transferring transit rights and military intervention in the Isthmus from Columbia to it.⁷⁶ The treaty was ratified in 1848, just as the need for an efficient transit route from the Atlantic to the Pacific increased with the California Gold Rush, with its attendant rise in global trade and labor immigration. In the absence of a viable plan to build the canal, the United States supported the construction of the Panama Railway, which provided an overland means of transporting goods across the territory and established the route the canal would later take. It opened in 1855, the same year the American engineer William Kennish proposed a plan to build a canal across the isthmus. Two French engineers, Armand Reclus and Lucien Napoleon Bonaparte Wyse, next surveyed the land, capitalizing on their recent success building the Suez Canal. The job was finally awarded in 1881 to the engineer who designed the Suez Canal, Ferdinand de Lesseps.

The story of the plans to make the canal, to this point, mirrors the great powers of the early modern world and their emergence into the new era of the nineteenth century: Spain, then Great Britain, France, and finally the United States entered the fray to determine who would gain the upper hand in the lucrative trade to be found in the “New World” of the Americas and the Far East. New only to Europeans, these areas became the arena in which the great colonial powers played out their attempts to dominate trade and transportation in an increasingly complex world. The complexity, and the unexpected challenge of new geographies, would be demonstrated in dazzling clarity by the struggles experienced by the attempts to build the Canal.

Ferdinand de Lesseps made two big errors in his proposal to build the Panama Canal, both of which were based on his poor understanding of the landscape and his lack of experience in tropical environments. The first, his commitment to building the canal at sea level, reflected the fact that he had only visited the site a few times and never during the rainy season. Thus, he was not aware that the Chagres River, which was the canal’s water source, became much more powerful in the 8-month long rainy season during which it rose about 10 meters: there was no way it could be channeled into a sea-level canal. He was caught off guard by the mudslides that accompanied the rains and forced workers to keep changing the angles of the slopes surrounding the canal to prevent it constantly being filled in with slide material. And he was consistently frustrated by the challenges that rain and constant humidity posed to

steel equipment and electronics. He was also not familiar with the significant changes in jungle fauna that accompanied the rains, such as the proliferation of venomous snakes, insects, and spiders. His second mistake was also related to his ignorance of the tropics: he did not know that the rainy season brought with it massive epidemics of malaria and yellow fever.⁷⁷ By 1884, approximately 200 workers were dying per month, and there was no clear understanding of how to prevent the deaths because the link to mosquitoes had not yet been established. The French effort went bankrupt in 1889, despite de Lesseps' best efforts to keep it alive, and lawsuits ensued surrounding the "Panama Affair." The project had cost 22,000 lives and lost the savings of 80,000 investors, costing approximately \$284 million US. While de Lesseps and his son were found guilty of misappropriation of funds, the sentences were later overturned and de Lesseps remained the engineering consultant for the new company that acquired the rights to the Canal and kept the construction site viable while also overseeing the railroad. The French manager of that company finally persuaded him that a sea-level canal was not viable, and that a lock and lake strategy was more practical.

The canal site stagnated as the new century began, but the United States began showing interest in purchasing the site or potentially establishing a new canal path in Nicaragua. The French management company dropped the price of the Panama Canal site considerably in the face of competition from Nicaragua, and in June 1902, the United States' Senate passed the Spooner Act, establishing the precedent for pursuing the canal across the isthmus if the necessary rights could be purchased. The project was threatened, however, by a civil war between the controlling Colombian troops and Panamanian rebels. The United States interceded in 1903, partially spurred by the French manager Bunau-Varilla's urging that the US support the Panamanian rebels and recognize their drive for independence. Roosevelt did so and ordered American warships to block sea lanes that would have permitted Colombian troops to put down the Panamanian rebels. Panama declared independence on November 3, 1903 and the United States was among the first to recognize it as an independent nation. Roosevelt quickly negotiated terms with the new ambassador to build and indefinitely manage and defend the Panama Canal Zone. The treaty was later condemned by many Colombians and Panamanians as infringing on the new nation's sovereignty, a fact that was underlined when Panama remained a US protectorate until 1939. In 1904, the United States officially purchased the French equipment, existing infrastructure, and control over the railroad for \$40 million, and paid \$10 million to Panama plus a guaranteed payment of \$250,000.00 in subsequent years.

American construction began immediately in 1904, and two big challenges faced the new engineering team: rebuilding the crumbling

infrastructure to build the canal and house the workforce; and attracting and maintaining a healthy workforce in the tropics. Both problems resulted from the brutally difficult and, for many Europeans and North Americans, alien natural environment. The reality facing workers moving into the Canal Zone was harsh. Worker quarters frequently flooded, food was monotonous and nearly impossible to keep fresh, and insects were everywhere. Tropical diseases were a daily reality, and keeping workers healthy was nearly impossible. The first effort to understand yellow fever was drawn from observations made by colonial physicians in other areas where the disease was endemic, such as French controlled Senegal and Spanish colonies in the Americas. In both places, it was observed that native adults rarely suffered from severe versions of the disease, while newcomers had very high rates of morbidity and mortality. This reflected the fact that those infected with the virus as children who survived were provided with immunity against severe forms of repeat infection. At the time, however, theories circulated that native people might be genetically capable of withstanding the disease, but there was no clear understanding of how it was transmitted.⁷⁷ The Cuban physician Carlos Finlay proposed that the vector for this disease was the mosquito, but that theory was not confirmed until 1900 and the virus itself was not discovered until 1901. This period of time also saw a proliferation of knowledge about tropical medicine, partially coming from investment in research by colonial powers and partially from the publication of research by western physicians working in tropical colonies. In 1898 and 1899, the British Colonial Office opened the Colonial Medical Service, Patrick Manson's book on tropical disease was published, and by the turn of the century, American and European labs had confirmed the vectors and modes of transmission of many tropical diseases, most notably yellow fever.⁷⁹ Thus the French effort to build the Canal took place with no strong direction for efforts to control yellow fever, while the American effort inherited an important piece of knowledge and combined it with existing public health efforts to control yellow fever. That said, it took the winning combination of American public health and Latin American knowledge about tropical diseases to keep the imported workforce healthy enough to build the canal.

The Public Health Service (PHS) was the organization tasked with managing sanitation and public health in the Canal Zone, a significant challenge given the environment and the lack of existing sanitation infrastructure. Among the tasks PHS officers undertook were quarantine of sick workers, the eradication of mosquito larvae and other pests, management of hospitals, and care of patients. Notable officers included Henry Rose Carter, who advanced understanding of mosquito-borne diseases, proposed means to eradicate them, and was appointed Surgeon General in 1915, and James Perry, whose work in quarantine in Panama led to

some of the first American reports on health conditions in Panamanian cities.⁷⁸ PHS officers worked alongside the medical wing of the Isthmian Canal Commission (ICC), which held responsibility for the entire canal project. They were led by William Gorgas, whose career highlights included establishing sanitation in Havana, Cuba where he managed first a typhoid and then a yellow fever outbreak during his service there from 1900 to 1902. He had first-hand experience demonstrating that sanitary control consistently correlated with political stability, and he set about establishing the former in the Canal Zone. The strict regulation of public health in the Canal Zone by ICC and PHS officers “transformed the Canal Zone and environs into a working laboratory where U.S. health officials had an enormous amount of power to study disease and enforce strategies of containment and eradication.”⁷⁹ The lack of sanitation in Panama City, especially in the poorest neighborhoods, made it into PHS reports, as did the lack of access to clean water and the prevalence of standing water providing breeding grounds for mosquitos. These reports provided important impetus to improve conditions in Panama’s cities, especially those for which the United States was suddenly responsible, but they also reflect the superior attitude of wealthy, educated, white Americans toward those they encountered with less education and darker skin, whether in the United States or outside of it. Many public health officers remained convinced that willful ignorance, rather than lack of access to better conditions, kept the poor struggling in terrible conditions. Thus, American efforts in Panama combined hygiene education with the installation and maintenance of sanitation infrastructure.⁸⁰ Mosquito brigades were an important part of this effort, because their primary job was to eradicate the pests carrying malaria and yellow fever, the two great killers of the Canal Zone. These brigades often combined American and Latin American public health workers, providing an important site of knowledge exchange in the fight against tropical disease.

The Panama Canal could not have been built without the mosquito vector theory proposed by the Cuban physician Carlos Findlay and confirmed by British and American laboratory scientists and public health workers. The success of this massive undertaking rested in the hands of Public Health Service and ICC medical wing staff who managed the day-to-day care of workers, established and maintained sewage systems and provided clean water, and eliminated pests. Finally, there could be no canal without the thousands of workers imported from the Caribbean to do the hard manual labor required to build a locks canal across mosquito-infested terrain. Paid in silver while American laborers, usually engineers, were paid in gold, housed in dismal structures with attention paid to their health only as it applied to their ability to work, these laborers’ bodies provided the data that became the basis for tropical

medicine in the twentieth century. Seen simultaneously as valuable for their labor and their status as medical subjects, these laborers – imported primarily from Jamaica and Bermuda – also became symbols of the racial and class biases embedded in colonial public health. Long after disease vectors were brought under control, vaccines were developed, and public sanitation in tropical cities established, these biases remained.

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4

THE GREAT INFLUENZA

A Virus for All Time

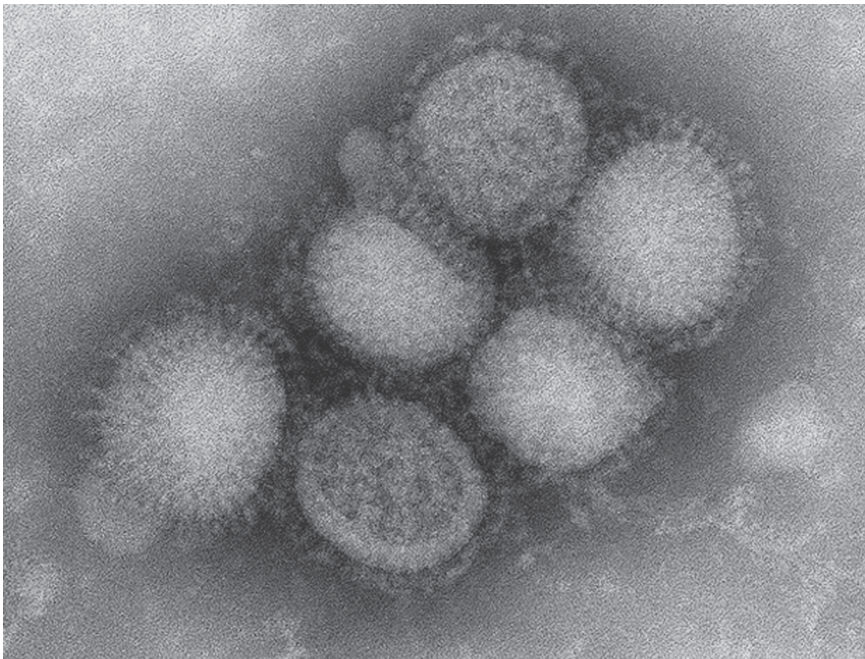


FIGURE 4.1 Electron micrograph of influenza.

Source: cdc.gov

CANADA GEESE – VIRAL RESERVOIRS IN FLIGHT

I grew up in western Canada in a family of readers and the public library was like a second home from the time I was in grade school. I loved browsing the shelves, choosing the stack of books I would lug home every 2 weeks. The fall that I turned 12, I was finally allowed to go to the library on my own, and I was walking home alone for the first time with my new stash of books. We lived in Saskatchewan then, on the edge of a new subdivision, and our street backed up to a wheat field. For the last few days, we had seen a large flock of Canada geese from our backyard, picking their way among the severed stalks, honking, grouping and regrouping, small clusters running forward and taking off for short flights before circling back to the ground. They were huge birds with their distinctive black heads and white chin straps, and they were loud, constantly calling back and forth. Our mum told us that the Canada goose mates for life and that the birds live in large family flocks. I'm sure she told us about migration, but I was completely awe-struck when I turned onto our street and saw the entire field of geese lift off at once. They formed a wide V above the field, flying higher and higher until all I could hear was the faint distant sound of honking. High against the pale blue sky, they powered away, finally disappearing into the horizon. The haunting sound of Canada geese in flight still fills me with awe.

Since that long ago day, I've been fascinated with bird migration, one of the most complex events in animal biology. It turns out that the pattern of regular seasonal movement between summer breeding and wintering grounds occurs in many species, prompted by decreasing food supplies as summer ends. The dwindling daylight photoperiod initiates endocrine changes which result in a massive increase in appetite and this leads to huge fat stores throughout the body, even around the eyes in geese. Then some critical combination of decreasing daylight and falling temperature prompts the beginning of the seasonal flight. Canada geese typically fly about 3000 feet above the ground at an average speed of about 40 mph, but they can fly much higher and have been clocked at speeds as high as 70 mph. During migration, they usually fly in the V formation that I witnessed, with each bird in line flying a little bit higher than the goose in front of it. The lead goose breaks the headwind, allowing the birds behind to "draft" along, making flight easier. Canada geese honk continuously during flight, and take turns as the leader, reducing fatigue for the flock as a whole. Migrations can be as long as 3000 miles, up to 1500 miles in a single day, navigating by a combination of inherent abilities including sensing the direction of polarized light from the sun and stars, detection of magnetic fields and visual and olfactory landmarks.

It is more than 50 years since my first sight of Canada geese in flight and there have been many reasons to change my feeling of unadulterated awe for

these magnificent creatures. The Canada goose has experienced major population explosions in areas throughout North America due in part to the success of wildlife management programs and in part to climate change, which has led birds to stay year-round in areas once too cold for wintering. If goslings do not experience migration in the first year of life, they never migrate, so enormous – and ever-increasing – flocks of geese have become permanent inhabitants of North American parks and golf courses in temperate areas that provide manicured lawns and ponds and lakes, the perfect landscape for comfortable Canada goose habitation. Alas, large numbers of geese means enormous amounts of goose droppings, almost 2 pounds per day for each adult bird, apparently a delicious treat for dogs but a source of frustration and disgust for human beings. In addition, nesting pairs are very protective and can be quite vicious in defending what they feel is their territory. And if all these issues were not enough, there is the problem of bird strikes, the collision of an aircraft with an airborne bird. Canada geese are among the birds known to be sucked into a jet engine where they can strike an engine fan blade, initiating a cascade which can result in engine failure. A 12-pound Canada goose striking an aircraft going 150 mph at lift-off generates the force of a 1000-pound weight dropped from a height of 10 feet, according to Bird Strike Committee USA. In 2009, a flock of Canada geese caused the crash of a US Airways flight just after take-off from LaGuardia airport. As documented in the 2016 film *Sully*, the pilot heroically guided the powerless plane to a safe landing on the Hudson River. Forensic analysis of remains in both engines confirmed that the birds were Canada geese. Although rare, the Federal Aviation Administration estimates bird strikes cost US aviation more than 400 million dollars annually and have resulted in over 200 worldwide deaths since 1988. I know these are all important issues but they have never been enough to dent my devotion.

It wasn't until I started to seriously study epidemics that I learned that Canada geese and other migratory waterfowl are the natural reservoir for the influenza virus. Somehow, knowledge that my Canada geese could have been the source of the virus that caused the infamous 1918 pandemic, the worst viral pandemic in known history, has given me a different perspective. Contemporary surveillance of geese along North American migratory routes has confirmed genetic virus diversity within birds in the migratory corridor. This means the birds can disperse new and potentially highly virulent influenza gene lineages all along their migratory route. Epidemiologists are terrified that this could be the source of a new pandemic strain ...

The Great Influenza: A Virus for All Time

Viral infections are the bread and butter of pediatrics because viruses cause the most frequent complaints that bring children in to see us: colds, ear infections and

gastroenteritis, the unpleasant combination of vomiting and diarrhea, known as the “stomach flu.” As these are usually not serious and no specific treatment is available, we reassure the parent and prescribe a variety of remedies to improve symptoms while the illness runs its course. I can hear myself now, cheerfully reassuring the exhausted mother of a cranky, sick child, “It’s only a virus.” The history of the deadly influenza pandemic of 1918 and the extended struggle science and medicine have waged to control the influenza virus reveal a much more complex and nuanced story.

By the early 1900s, knowledge of the germ theory of disease had already begun to transform public health sanitation practices like water treatment and sewage disposal, and improved personal hygiene practices like handwashing and safe food preparation. While antibiotics as specific treatments for bacterial infections did not appear until much later in the twentieth century, comprehension of the germ theory had already resulted in major public health improvements that significantly decreased deaths from infectious diseases.¹ In this setting of increasing scientific knowledge and improving public health, viruses were still virtually unknown. *Bacteria* were the “germs” of the germ theory and their identification as the specific causes of infectious diseases was the major focus of science and medicine.² In the late 1800s, viruses had been identified as infectious, submicroscopic organisms that were obligate intracellular parasites, capable of replication only in a plant, animal or human host. By the time the 1918 influenza pandemic occurred, very little more was known: viruses were a mysterious group of tiny microbes that were infectious, filterable and required living cells for replication, but their structure and function remained unknown.³

Influenza, however, was well known. Major outbreaks of influenza had occurred throughout recorded history, beginning as early as 412 BC. There were increasing reports of flu epidemics and pandemics from the late fifteenth and early sixteenth centuries into the eighteenth century and with at least three pandemics in the nineteenth century, the last of which occurred from 1889 to 1893 and extended from Russia to Europe, England and ultimately the Americas. This pandemic, called the Russian flu, was the first to be rapidly spread by people traveling on trains and steamships, an early example of the important role of interconnection in disease transmission. By the time of the deadly influenza pandemic in 1918, the unidentified influenza pathogen had a long history of causing devastating disease.

The Disease

Even in the early 1900s, the typical influenza or “flu” infection was well recognized, characterized by nasal and airway congestion, cough, fever, chills, joint and muscle pain, conjunctivitis, headache and extreme fatigue. It is highly contagious, spread from one person to another in three main ways: by direct transmission, when an infected person coughs or sneezes into the face of another person – a route that is highly favored by children; the airborne route via inhalation of virus-contaminated air; and through hand-to-eye, -nose, or -mouth transmission, from contaminated

surfaces or direct personal contact. The airborne route is the most important because the average sneeze or cough can send as many as 100,000 contagious viruses into the air at speeds up to 100 miles per hour to a distance of 6 feet.⁴ Surfaces can be contaminated and small pathogens like the tiny influenza virus can remain suspended for hours to days, so the opportunities for infection from a single unprotected sneeze are substantial!

Symptoms begin 1–2 days after infection and usually last 1–2 weeks; they can be very mild, but most adults can remember experiencing a bad flu attack when they were so achy and weak and sick that they had to stay in bed for days. Infected individuals – even those without symptoms – shed the virus for 7–8 days. Even in uncomplicated cases, cough and fatigue can last as long as 2 weeks. Influenza is much more serious in those with underlying lung or heart problems and a small but significant number of people develop a secondary pneumonia, which can be very serious.⁵

Influenza viruses infect the epithelial cell lining of the entire respiratory tract – from the nose, through the throat, into the trachea and bronchi to both lungs – and begin replicating immediately after arrival, peaking after 48 hours. Mild cases show pathological changes only in the upper and lower respiratory tracts, but severe cases show clear evidence of pathologic changes of air space disease/pneumonia in the lungs. Not surprisingly, most pathologic information comes from severe cases with direct pulmonary involvement. In typical, self-limited disease, the tracheobronchial changes of influenza infection can be summarized as redness and inflammation with mucopurulent discharge; microscopically, there is destruction and shedding of the pseudostratified epithelium of the inflamed trachea and bronchi, leaving just the basal layer intact. As the infection subsides, the epithelium is regenerated, a process that can take up to a month.⁶

The symptoms of influenza reflect a combination of direct effects of the virus on respiratory epithelial cells and systemic symptoms from the elaboration of cytokines, cell signaling molecules that aid cell-to-cell communication in immune responses and stimulate the movement of cells towards sites of infection. Following primary exposure, cytokine inflammatory responses are triggered when infected cells die, increasing blood flow, and bringing plasma and leukocytes (white blood cells) to the site of injury, elevating local temperatures, and causing pain. The acute inflammatory response is also marked by the activation of pro-inflammatory cytokines including interleukin-6 (IL-6), type 1 interferons, and tumor necrosis factors (TNFs) like TNF-alpha; a combination of these factors is considered to be responsible for the respiratory tract symptoms of pain, congestion and cough plus systemic symptoms of fever, muscle pain, headache and exhaustion. Increasing inflammation is accompanied by immune cell infiltration and tissue damage. As the infection subsides, the epithelium is regenerated; in most cases, function can be completely restored by this reparative process.⁶

Cytokines are central to the induction of the body's immune response to viral infection via activation of specialized white cells including natural killer (NK) cells, white cells which are part of the innate immune system, mediating

the initial response to infection by responding quickly to detect and kill virally infected cells. The innate immune system attempts to limit a viral infection immediately, before the adaptive antigen-specific immune response is engaged. The antigen-specific response to infection is mediated by T cells (thymus cells) and B cells (bone marrow- or bursa-derived cells), the major cellular components of the adaptive immune response. T cells are responsible for cellular immunity, a protective immune response that involves activation of phagocytic white cells and the release of cytokines and chemokines in response to a viral invader. B cells proliferate and secrete large amounts of virus-specific antibodies. These antibodies bind to the surface of the viral antigen which is then identified for elimination. Once virus-specific antibodies are created, they persist and will bind to the surface whenever that specific virus is re-introduced, preventing future infection.^{7,8}

These days, mortality from the flu averages less than 1%, usually in the elderly or those with underlying lung disease. Based on autopsy studies, about one third of people who die from flu-related causes expire because the virus overwhelms the immune system; another third die from the response to secondary bacterial infections, usually in the lungs; and the remaining third perish due to the failure of one or more other organs. According to the World Health Organization: "Every winter, influenza occurs globally with an annual attack rate estimated at 5%–10% in adults and 20%–30% in children. Worldwide, these annual epidemics are estimated to result in about 3 to 5 million cases of severe illness, and about 250,000 to 500,000 deaths."⁹ The attack rate is defined as the proportion of those who become ill after a specified exposure: for the influenza virus, the true asymptomatic fraction is difficult to define, varying from a low mean of 16% in outbreak investigations to as high as 85% in longitudinal studies where infection was defined using serology.¹⁰ It is safe to say that a significant proportion of those who are infected with the influenza virus develop a symptomatic illness.

The flu occurs in the cold season in both hemispheres: in the Northern Hemisphere from October through April, and in the Southern Hemisphere from April to September. Why influenza appears primarily in winter conditions is still not entirely understood. The virus does survive longer in cold, dry conditions and in light of direct person-to-person transmission, clustering of people indoors in the winter is also thought to be a factor, but the complete explanation for seasonality of influenza remains obscure.¹¹ Historically, one of the most challenging features of influenza is that the expression of the disease is highly variable between seasons. In many years, the flu can be little more than a bad cold, but intermittent pandemics with severe morbidity and much higher mortality have swept the globe in every century since recorded time.

The Great Influenza: The Global Influenza Pandemic of 1918

There are three essential requirements for a global pandemic to occur: emergence of a new agent that infects humans; little or no population immunity to that agent; and easy pathogen transmission from one person to another – typically, this means

airborne transmission. In 1918, a new hyper-virulent strain of influenza with all these characteristics emerged and the subsequent pandemic that it caused was one of the worst natural disasters in history. The exact site of origin of the pandemic is unknown, but two commonly cited countries are the United States and China. The American story reflects the time when the United States entered World War I in the spring of 1917. Mobilization ultimately included a military draft of all men aged 18–35 years who were shipped over to Europe as fast as they could be trained. More than 4,000,000 military personnel were in frequent, close contact during training in the USA and transport to and from the battlefields of Europe, a perfect setting for person-to-person disease transmission. As described in detail by John Barry in his excellent book *The Great Influenza*¹² and summarized here, there was a sudden outbreak of severe influenza in Haskell County, Kansas, reported by a local physician to the US Public Health Service. With a constant flow of traffic between Haskell County and Camp Funston, a nearby major military training facility, it was only a month before the first case of influenza was reported there. Within 3 weeks, more than 1100 men were hospitalized on the military base with influenza, and thousands more were treated as outpatients, confirming the ease of human-to-human pathogen transmission, especially in close quarters, and the general absence of immunity to this virus. In Kansan civilians, the first wave of influenza ended by mid-March but the military outbreak – fueled by incoming recruits – continued at Camp Funston into the late spring. When American soldiers began arriving in large numbers on the Western front in Europe early in the summer of 1918, the theory is that they carried the influenza virus from this first wave of disease with them.

The story of a Chinese origin for the virus is also very intriguing. In November 1917, a severe, contagious respiratory disease of unknown origin was reported in northern China. Characterized by fever, cough, congestion, headache and muscle pain, it was variably diagnosed as “pneumonic plague” and “winter sickness” and was reported to have high mortality. Despite efforts by Western doctors, no diagnosis was confirmed before the outbreak ended in the spring of 1918. Meanwhile, during the winter of 1917–18 on the Western Front in Europe, manpower among the British troops was critically low so arrangements were made to mobilize men from the Chinese Labor Corps (CLC). Desperate for manpower, the British Government recruited nearly 100,000 Chinese laborers to support their troops on the Western Front. Recruitment took place in the interior of northern China, in the area where the strange respiratory disease had been reported and there were newspaper reports of “pneumonic plague” in the transport camps of the CLC. Ultimately 25,000 Chinese workers were transported to the front around this time, either by ship directly to Europe around the horn of Africa, or by ship to Vancouver, across Canada by train, and then across the Atlantic to France.^{13,14} Based on British and Canadian War Diary reports from January through September of 1918, many of the Chinese men had to be hospitalized with “purulent bronchitis” and there was a high mortality rate associated with this illness.

Meanwhile, back in China, the respiratory disease seen in the winter of 1917–18 recurred the following autumn, and this time it was diagnosed as “Spanish

Influenza,” the name given to influenza in Europe. While influenza was subsequently widespread in China in 1918–19, the disease was mild in many places compared with elsewhere in the world with a much lower mortality rate, suggesting that population immunity may have been higher than elsewhere in the world.¹³ This raises the possibility that the 1918–19 influenza virus originated in China in the winter of 1917 and was carried to France by Chinese migrant workers. Given what we know now about how often new highly virulent influenza viruses arise in China, this is a compelling theory.

Regardless of the country of origin, the next wave of influenza was disastrous and involved multiple sites.¹⁵ It began in mid-summer of 1918 with sporadic reports of clusters of very severe influenza cases from England, Europe and the United States, characterized by sudden onset, often progressing rapidly to severe respiratory distress with hemorrhage from the lungs, nose and ears. While death from usual seasonal influenza was (and is) rare, mortality from this outbreak was high from the outset. At autopsy in these cases, the normal architecture of the airways and the lungs was found to be destroyed in a pattern never seen before with influenza. The excess influenza deaths involved two overlapping clinical pictures: one pattern was the rapidly evolving severe respiratory distress pattern associated with acute airway destruction; the second pattern was an aggressive secondary bacterial pneumonia which began a few days after the onset of the flu.⁶

Among European countries, Spain was one of the earliest to be hit hard by the disease and one of the few with open reporting, leading to the designation of the disease as the “Spanish flu.” In early August, there was a report from Switzerland of an epidemic of influenza in Switzerland called “the Spanish sickness.” At that same time, army training sites in the US were reporting flu outbreaks of increasing severity and number, and several outbreaks occurred on naval steamships docking in Canada and the United States.

Then, in late August, major outbreaks were reported simultaneously in multiple military transport sites: in western France in the major harbor city of Brest where multiple naval ships dropped new recruits from the US; in Freetown, Sierra Leone, a major coaling center for military ships on the western coast of Africa; and in Boston harbor, on board a massive receiving ship where military personnel in transit were housed.¹⁵ In each of these sites, the disease struck suddenly and severely and the number of influenza cases rose exponentially. In Boston, by the first week of September, the outbreak had spread beyond the military ship with influenza cases reported in civilians, and this was followed by an overwhelming outbreak at Camp Devens, a military camp which housed 40,000 men just outside the city. Barry reports that in a single day, more than 1500 men reported ill with influenza.¹² The disease followed the pattern of sudden onset and for most patients, went on to an influenza-like illness that was transiently very debilitating but not usually fatal. However, despite the best efforts of military medical teams supported by the Red Cross, more than 100 men died each day, so many that a special barracks was set aside as a morgue. The hospital was overwhelmed with hundreds of young soldiers packed together on makeshift cots along with stricken doctors and nurses. The

hospital was designed to treat 1200 patients, but at the peak of the outbreak, more than 6000 soldiers were crammed in, coughing, bleeding and dying. Influenza cases were quarantined at their military camps, but this did nothing: the disease exploded in cities and towns all over the country.¹⁵

In the civilian US population, the epidemic swept down along the east coast from Maine to New Orleans, inland into the Midwest and, eventually, the west coast. Thousands were desperately ill and hundreds in each town and city died as federal, state and municipal governments struggled to find ways to help the sick and take care of the bodies of the dead. Doctors and scientists put all their efforts into finding some way – any way – to treat this terrifying version of a disease they thought they understood. The virus ultimately sickened tens of millions of people in the US. After a week to 10 days of misery most recovered, but 10–20% of victims suffered from the intensely virulent, fatal form of the disease with extreme fever and chills, bleeding from the lungs, nose and ears, profound shortness of breath and cyanosis of the face and extremities due to hypoxia, with pockets of air under the skin due to rupture of the lungs. As in the fatal cases earlier in the outbreak, autopsies showed that the architecture of the airways and the lungs was destroyed.^{6,16}

Strikingly, the death toll was worst in three age groups – infants and the elderly, as usually seen with virulent pneumonia – but mystifyingly, also in previously healthy young adults. In those who survived the acute onslaught of the virus, the disruption of the airways and lung tissue allowed invasion by colonizing strains of bacteria. In subsequent clinical and immunologic studies of severe influenza, an excessive inflammatory reaction has been described with markedly higher levels of the proinflammatory cytokines including interferons, TNFs, interleukins and chemokines that are part of the typical immune response in all influenza cases. Called a “cytokine storm,” these dramatically elevated cytokine levels have been shown to correlate directly with tissue injury and an unfavorable prognosis in severe influenza cases.^{17,18} Overall, the synergistic direct effects of aggressive primary infection with the virus, secondary opportunistic bacterial pneumonias and the induction of cytokine storm are felt to be responsible for the high mortality. Because the immune response is maximal in healthy young adults, the excessive inflammatory reaction is thought to be the reason for the high mortality in that age group. The number of deaths worldwide was estimated to be at least 50 million with approximately 675,000 occurring in the United States. More Americans died from influenza than they did during all of World War I.

As influenza ravaged the United States, it appeared simultaneously all over the world. From Alaska through Mexico to South America, from Iceland across all of Europe into the Middle East and down through all of Africa, from the Mediterranean to India and the Far East: the death toll was at least 10% overall, far above the usual 1%, but dramatically higher, as high as 25%, in native populations whose immune systems had presumably never been exposed to influenza viruses of any kind: Native Americans and Canadians, Inuits, Pacific Islanders and Africans. A very few isolated settlements who were able to maintain isolation were spared, but overall, virtually

all of civilization was threatened. In India alone there were at least 20 million deaths, and worldwide more than 50 million people died. More people died of influenza in a single year than in the infamous “Black Death” bubonic plague from 1347 to 1351. It is still one of the worst pandemics in recorded history.¹⁹

However, the virus appeared to become spontaneously less lethal as the epidemic continued and this was seen in the lower death rates in American cities which presented with disease later in the course of the pandemic. At the same time, survivors of the disease had developed immunity and without new hosts, the virus – and therefore, the epidemic – died out. In general, the cycle from the first case of influenza to the final case lasted 6–8 weeks. By late November of 1918, the pandemic was over. There was a weak third wave in the winter of 1919 and again in 1920, but the terrifying influenza pandemic of 1918 was effectively over within 3 months of its precipitous onset. The pandemic contributed significantly to the ultimate collapse of an already weakened Germany and thereby to the end of the war, with peace declared on November 11, 1918, just as the pandemic began to wind down.¹⁵

World War I presents a unique opportunity to observe the impact of globalization on the spread of an infectious disease, beginning with the critical role of travel. Never before had so many people traveled so rapidly and so widely around the world to a common site. Both the major theories of influenza introduction featured international travel from remote sites – middle America or northern China – to the battlegrounds of Europe via trains and crowded transport ships. Never before had the population density been higher than in the European conflict zones, where men from all over the world were brought together. In numbers alone, more than 10 million men had been mobilized to the battlegrounds of Europe by the end of the war, primarily from colonies of the British Empire but also including 4 million Americans. Troops were packed together in trenches, bunkers and tents and consequent overcrowding mandated close interpersonal contact among whole battalions of men. With an airborne virus like influenza, rapid pathogen transmission was almost guaranteed. And never before had a pathogen had such a wonderful opportunity to hitch international rides on people, boats and trains. As the war wound down, soldiers who were transported home on crowded transport ships and trains carried the virus with them and transmitted the infection virtually all over the world. The extensive global spread of the 1918 influenza virus dramatically exemplifies the critical role of global interconnectedness in pandemic disease spread.

The impact of the epidemic at home is shown dramatically by considering the average life span in the United States between 1900 and 2000. Life span is a reasonable measure of the overall health of a population and is a primary indicator of the effect of disease and health care on mortality, but it also reflects the state of nutrition, housing and health education. The importance of these other factors is apparent when we look at the difference in lifespan between whites and blacks: in 1900, the average life span in the United States was 47 years in white men and 33 years in black men; for women, the average life span was 49 years in white women compared with 34 years in black women. The dramatic increase in average

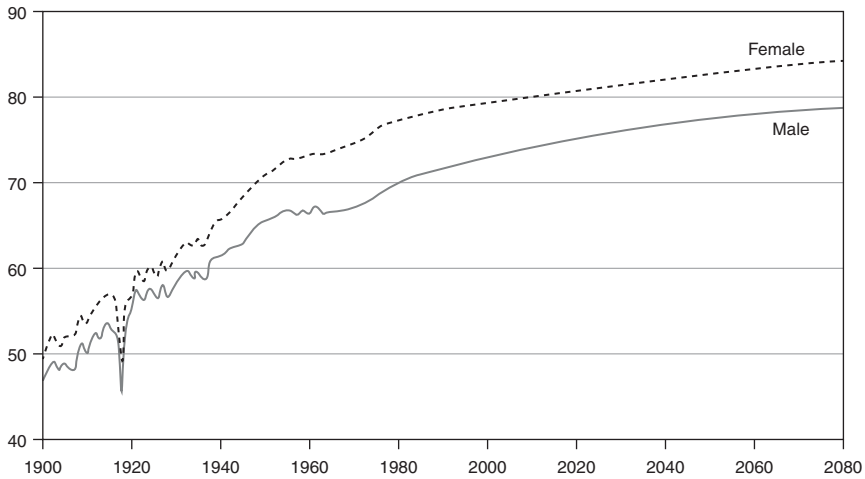


FIGURE 4.2 Median age at death by gender and calendar year: 1900–2100. US Social Security Administration, SSA.gov.

Available from: www.ssa.gov › oact › NOTES › as116_V. Accessed 3/3/2017

life expectancy in the US during the twentieth century is shown graphically in Figure 4.2.²⁰ The sharp decrease in life expectancy in 1918 and 1919 reflects the large number of young people who died of influenza, a large enough number to decrease average life expectancy for the whole population by almost 10 years! You can also see that as the century progressed, life expectancy increased dramatically. By 1950, the average age at death for white men and women was 67 and 72 years, respectively, a mean increase of 43%. The gain was even greater in blacks, to 59 years in black men and 63 in black women, a mean increase of 79%. There were further gains in the second half of the century, overall a mean 61% increase for White Americans and 106%(!) for Black Americans.

The Virus: The Long Road to Discovery

As the twentieth century began, more and more diseases were linked with specific bacteria, and although antibiotics were not yet available, vaccines had been created for selected infections. There was increasing appreciation of the role of immunity and tests for disease-specific antibodies were becoming available. The practice of medicine was beginning to rest on a scientific base. At the same time, understanding of the importance of hygiene and sanitation led to an increasing role for public health in everyday life. Against this backdrop, influenza emerged as a sudden and terrifying wave of disease and death. Compared with usual seasonal flu outbreaks, this illness was characterized by its acute, severe onset, by progression to lung involvement in a significant subset of cases and by a much higher mortality rate, especially in young adults. In fatal cases, there was progressive respiratory

distress and then septic shock leading to death. Doctors had little to offer except oxygen, fluids, rest and prayer.

During the influenza epidemic of 1892, a scientist named Richard Pfeiffer isolated a small, rod-shaped bacterium from the noses of flu-infected patients; he believed this was the cause of influenza.²¹ The bacteria was named *Bacillus influenza* but became known as Pfeiffer's bacillus, and when the influenza pandemic began in 1918, most physicians and scientists believed this bacterium was the cause of influenza, in line with the germ theory that specific bacteria cause specific diseases. Because of the gravity of the illness and the severe lung involvement, there was an intense focus on confirming the cause for influenza, with doctors collecting blood and sputum cultures on every patient, hoping to identify Pfeiffer's bacillus or another known bacteria as this would potentially allow development of antisera and vaccines that could protect against the infection; antipneumococcal serotherapy was in its infancy but could theoretically have been employed if a type-specific bacterium was identified.²² Despite these efforts, neither Pfeiffer's bacillus nor any other bacterium was consistently identified in flu victims – more commonly, multiple known bacteria including *Streptococcus* and *Pneumococcus* were found in patients with secondary pneumonia complicating the flu.⁹ Despite the enormous number of cases and the extensive efforts of doctors and scientists, no cause for the 1918 influenza pandemic was discovered at the time.

The search for a cause continued after the pandemic ended. In 1919, scientists from Japan and from France reported separately that a bacteria-free emulsion of mucus or blood from influenza patients produced classical flu symptoms of varying severity when given to monkeys and to human medical volunteers.^{23,24} These results strongly suggested that influenza was caused by a virus, but scientists were unconvinced, perhaps because at the time so little was known about the basic nature of viruses. Viruses were defined by two negative characteristics: they were not retained by standard bacteriologic filters and they were not visible by light microscopy. They could only be identified by inducing disease in a susceptible plant or animal with a bacteria-free filtrate from a diseased subject, or indirectly, by detecting the presence of serum antibodies against the disease in survivors of the illness in question. Using these methods, viruses had been confirmed as the cause of a number of human and animal diseases including smallpox, yellow fever, rabies, measles and polio.

It was 1933, 15 years after the influenza epidemic ended, before scientists in the United States (Richard Shope, studying swine flu) and in Britain (Wilson Smith, Christopher Andrewes and Patrick Laidlaw, studying flu in ferrets) showed convincingly that influenza was caused by a virus and that this virus infected many different animals. The ability of a single virus to infect both humans and animals was a previously unrecognized feature of the armamentarium of viruses that would prove to be critically important in understanding the ability of viruses to evolve and to infect.^{25,26} Confirmation that influenza was caused by a virus was followed immediately by attempts to develop a vaccine against the virus since the concept of immunity was well-developed by the 1900s and antitoxins and vaccines against diseases like smallpox, diphtheria, tetanus, anthrax, cholera, plague and typhoid had

already been developed. All influenza was thought to be caused by the single virus identified in 1933, so vaccines were developed to prevent infection with this specific virus. It was these attempts at vaccine development that revealed one of the most important traits of the influenza virus: the capacity for spontaneous mutation. When a vaccine developed by Smith and Andrewes using the 1933 virus that had been effective in laboratory animals was a complete failure in humans in the 1936 flu season, they and other researchers recognized that significant variation in the virus must have occurred between flu seasons.^{27,28} Spontaneous mutation is one of the most powerful weapons of the influenza virus and its identification was a major step forward in understanding its virulence.

The start of World War II led to concerns about another wartime pandemic, so vaccine development took precedence over pure laboratory investigation. Thomas Francis and Jonas Salk, two of the American scientists whose work ultimately led to creation of the polio vaccine, developed an inactivated influenza vaccine by injecting the virus into chicken eggs, where it multiplied, producing high antigen concentrations which they used to induce immunity.²⁹ This vaccine was shown to be safe but only modestly effective. In 1940, a second type of influenza virus was identified from individuals with what appeared to be typical, seasonal influenza: the original virus was named influenza A and the new virus, influenza B. Ultimately, unlike the type A flu virus strain, type B was found to exist only in humans; it causes a typical flu illness but does not cause pandemic disease. From 1942 onward, all flu vaccines have contained antigens against both A and B strains. Antibody titers in response to the inactivated vaccine showed good theoretical protection against both viruses but clinical protection against seasonal influenza remained limited, presumably reflecting the spontaneous variation of the virus. Ultimately, four major strains of influenza virus were identified, A, B, C, and D. Influenza A and B strains are responsible for seasonal flu outbreaks every winter but only influenza A strains have caused pandemic disease. Influenza type C generally causes only a mild respiratory illness and influenza D viruses do not cause disease in humans. As the cause of pandemic disease, influenza type A is the focus of this chapter.

In 1935, the electron microscope (EM) gave us our first images of viruses, revealing their simple basic structure: a protective protein shell around a nucleic acid core of genetic material, as described in Chapter 1.³⁰ Using a bacteriophage, a kind of virus that only infects bacteria, a simple description of viral replication was developed. Outside of a host a virus was metabolically inert, but once connected to a host cell the virus inserted its genetic material and took over the cell's functions. New viruses were formed, self-assembled and burst out of the host cell, killing that cell and going on to infect others.³¹ A critically important discovery was also made using a bacteriophage when two virus particles simultaneously infecting the same cell were seen to exchange parts of their strings of genes resulting in new, hybrid forms of the original viruses – a process called recombination.³²

In 1945, the influenza A virus was first visualized by electron microscopy and was found to be one of the smallest viruses identified to that time.³³ The virus was described as roughly spherical, and only 80–120 nanometers in length (Figure 4.1).

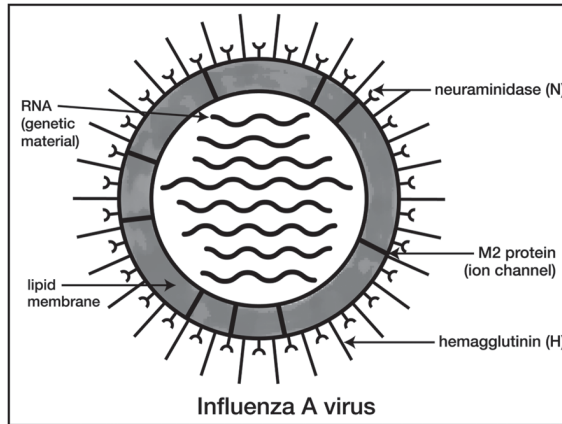


FIGURE 4.3 Graphical image of influenza A virus with surface glycoproteins and interior displayed.

Source: cdc.gov

Subsequent more sophisticated EM analyses have clearly shown a degree of pleomorphism, with the native virion morphology including spherical, elliptical, and filamentous forms.³⁴ Early EM examination using negative staining techniques revealed the virus to be covered by spiky surface projections of two distinct types – hemagglutinin (HA) and neuraminidase (NA) – and electrophoresis showed these to have different biologic activities.³⁴ Subsequent imaging by cryo-EM reveals HA to be a membrane glycoprotein shaped like a drumstick with a globular head on a broad stem. Influenza NA is a glycoside hydrolase enzyme seen as a mushroom-shaped projection with the cap composed of four spherical subunits, as shown in Figure 4.3. On the surface of the virus, the ratio of HA to NA is approximately four to one and these two surface proteins are accompanied by a much smaller number of a third membrane protein (M2) which is a matrix ion channel.^{35,36}

Complete knowledge of the process of cell infection is still evolving, but HA and NA were found to be critically important components in the influenza virus. To summarize what is a far more detailed process, HA binds to a sialic acid receptor on the surface of host cells and mediates virus attachment to the cell surface. NA then cleaves sialic acid from the viral receptors, allowing the virus to enter the cell by endocytosis. HA mediates release of the genome into the host cell nucleus by pH-dependent membrane fusion. After transcription and replication, a series of steps allows progeny virions to be assembled and NA accelerates their release from the host cells.^{34,37}

After deoxyribonucleic acid (DNA) was identified as the carrier of genetic information and the double helix structure of DNA was recognized, ribonucleic acid (RNA) was also recognized to be a carrier of genetic information.^{38–42} In 1986, the influenza virus was found to be a single-stranded RNA virus with eight segments.^{43,44}

This discovery had major implications for understanding variation in influenza viruses. Spontaneous mutations, including substitutions, deletions, and insertions of single nucleotides, were found to be one of the most important mechanisms for producing variation. Such point mutations were a characteristic common to all cells, bacteria and viruses. With this kind of mutation, small, subtle changes occur randomly and are incorporated into the viral genome, a process called *genetic drift*. Mutation rates differ significantly between DNA and RNA viruses: RNA viruses like the influenza virus have very high mutation rates, approximately one mutation per genome copy, because lack of proofreading by RNA polymerases allows multiple replication errors.⁴⁵ (By contrast, there is much higher replication fidelity found among DNA viruses.) Each round of RNA virus replication results in a mixed population with many variants, most of which are not viable, but some of which have potentially advantageous mutations that allow the mutant to survive and even become dominant under the right selective conditions. Only mutations that do not interfere with essential viral function survive, but the high mutation rate in RNA viruses provides many opportunities for this to occur. Genetic drift results in literally thousands of lineages and sublineages of influenza viruses.

Recombination – the process of two virus particles infecting the same cell exchanging parts of their genetic material to produce new hybrid forms of the original viruses – was first described in 1936 and was subsequently found to occur primarily in DNA viruses; it was recognized as resulting in new viral strains which could infect previously resistant hosts. A particular form of recombination called “reassortment” was found to occur only in segmented RNA viruses, like the influenza virus. Whole segments of genetic material could be exchanged between viruses infecting the same cell, resulting in progeny with immediate and major antigenic change.⁴⁶ Based on findings like these, it was recognized that the process of genetic information exchange by reassortment can occur between animal and human strains of a virus and can result in an entirely new and antigenically novel virus strain. In a single influenza virus replication cycle, a potential killer virus can emerge, highly infectious, easily transmittable and lethal. Endless evolution by both spontaneous mutation and by genetic reassortment results in the continuous emergence of new, antigenically novel influenza virus strains to which human hosts can have limited or no resistance.⁴⁷ These findings provided powerful insight into the infectious potential of the influenza virus.

It is with the surface proteins HA and NA that the results of continuous mutation in the influenza virus – by drift or by shift – are most powerfully expressed. HA and NA are the major determinants of influenza A infectivity, transmissibility, pathogenicity, host specificity and antigenicity. The receptor binding residues of influenza A are located in the HA head domain. In viral hosts, cell surface receptors vary substantially between host species as well as in target tissues and cell types of the same species, leading to variations in the HA-binding capacity of circulating viruses. Therefore, receptor specificity plays an important role in viral cell and tissue tropism, interspecies transmission and adaptation to a new host. Spontaneous point mutations in HA can alter the sialic acid receptor specificity on potential host

cells and thereby alter the antigenicity, host range, replication efficiency and pathogenicity of the virus. Inability of variant strains to bind with surface receptors is an important mechanism limiting the emergence of new pandemic strains. Host range and virulence are also the result of optimized molecular interactions between viral HA, NA and cellular factors. Together, HA receptor-binding mutations and NA activity-enhancing mutations are critically important mediators of influenza A cross-species infection.⁴⁸ Using serologic tests with hyper-immune serum, a total of 18 HA subtypes (H1–18) and 11 NA subtypes (N1–11) have been found in nature. Influenza A virus subtypes are classified based on the sequence and antigenic divergence of the HA and NA surface proteins on the surface of the viral envelope. The US Centers for Disease Control and Prevention (CDC) follows an internationally accepted naming convention for influenza viruses beginning with the antigenic type (A, B, C); the geographic site of origin; the strain number and the year of identification. The influenza A virus is identified specifically by description of the hemagglutinin and neuraminidase antigens in parentheses.³⁶

Return of the Canada Goose

By this time, migratory water birds, including specifically (my beloved) Canada geese, had been shown to harbor a large number of different influenza A virus strains.⁴⁹ Ultimately, wild aquatic birds – particularly Canada geese, wild ducks, swans, gulls, shorebirds and terns – were identified as the natural hosts of the influenza virus and the source of all influenza viruses in other species. Enormous pools of influenza virus strains were found to continuously circulate in these wild birds, providing a stable evolutionary reservoir of viral gene sequences available as potential recombinants for introduction into human populations.⁵⁰ Genetic analyses reveal that antigenic drift of the influenza A virus takes place at a much lower rate in wild birds than it does in other host species. The strains that exist in wild birds appear to be in relative evolutionary stasis, as shown by the fact that strains collected from wild birds many decades apart were virtually identical. This implies that an optimal host–parasite relation has been reached and that any change in genetic make-up will result in fewer functional strains that will not survive. In these water birds, the virus is non-pathogenic and lives in the gastrointestinal tract, excreted continuously in the feces. Water sources that are homes for aquatic birds are infected and this is a natural source for virus transmission from one bird or animal to another.

Aside from humans, the influenza A virus has also been found to infect a wide variety of other mammalian species, including all marine mammals, pigs, horses and New World bats. This wide host range is part of the reason that influenza viruses have shown so much genetic diversity over time because extensive spontaneous antigenic mutation occurs continuously in each mammalian host. All 18 HA subtypes and 11 NA subtypes have been found in nature. Viruses of all known subtypes except H17N10 and H18N11 are maintained in aquatic birds, but only a subset of HAs (H1, H2, and H3) and NAs (N1 and N2) naturally circulate in humans. Subtypes H17N10 and H18N11 have been found only in bats. New

influenza virus subtypes with minor but cumulative antigenic variations emerge constantly by spontaneous mutation from the wide number of animal reservoirs, and it is these new subtypes which are responsible for the annual occurrence of new influenza virus strains. By contrast, major new influenza strains with pandemic potential arise only rarely from reassortment between a human flu virus and strains from avian reservoirs plus or minus additional animal virus strains, producing an entirely new virus subtype with previously unseen HA and NA antigens.⁵⁰ Human and avian strains of the influenza virus both replicate well in pigs, which represent an important intermediary in viral mutation: when the same pig cell is infected with multiple avian and human and/or animal viruses, genetic exchange between the strains can reassort to produce antigenically unique and potentially highly virulent offspring which can appear suddenly, in a single infectious cycle.⁵¹ This allows no opportunity for immunity to develop or for preventive vaccines to be created and guarantees accelerated disease spread. All known influenza pandemics in recent human history have been caused by viral subtypes which emerged after reassortment of genes from the H1N1 human virus plus avian and/or other animal sources.

Global Influenza Pandemics After 1918

It took many decades for the true infective armamentarium of the influenza A virus to be appreciated. Because it is an RNA virus, there is ongoing continuous mutation by genetic drift. The influenza virus is segmented and infects multiple species – this allows reassortment to occur with unique combinations of animal and human gene segments emerging as highly virulent reassortants. The combination of genetic drift and shift means entirely new strains of the virus that infect humans arise constantly. Because these are entirely new strains, there will be little or no population immunity, and the influenza virus is airborne, ensuring widespread transmission from one person to another. Little wonder scientists and physicians have been haunted by the fear that another strain like the one that caused the 1918 pandemic Spanish flu could emerge at any time. In 1947, these concerns prompted the nascent World Health Organization (WHO) to establish an international influenza surveillance program called the World Influenza Center. Originally based in the National Institute for Medical Research in London where Andrewes, Smith and Laidlaw had carried out much of their work, the center was responsible for coordinating influenza surveillance efforts, carrying out and coordinating laboratory work on influenza, and training new laboratory workers. By 1952, it was clear that a worldwide network of laboratories was needed to optimize surveillance and support countries without existing viral laboratory capacity and the WHO established the Global Influenza Surveillance Network, tasked with determining which influenza strains to include in the next year's vaccine.

Then, in February 1957, a completely new strain of influenza A with previously unknown HA and NA did appear, originally in China. Despite all ongoing surveillance efforts, it was not identified in advance by scientists or viral researchers.

The known influenza A virus was re-labelled H1N1 and the new strain as H2N2. Immunity to this new strain was rare in people less than 65 years old and the existing vaccine offered no protection at all: experts predicted a major pandemic of this Asian flu, and they were not disappointed. In the first months of 1957, the virus spread throughout China and the Far East and by midsummer reached the United States. Although the concept had already been proven, it was this pandemic that clarified the importance of new hybrid viruses formed by reassortment in cells infected simultaneously with different influenza viruses from different species. The H2N2 virus was ultimately found to be the product of reassortment between an influenza virus from wild ducks and the circulating human influenza virus strain, with three gene segments from the avian influenza gene pool combined with five from the human strain.⁵² A new vaccine was emergently developed but production took many months while infection rates waxed and waned through the fall and winter. H2N2 influenza-related deaths were maximal between September 1957 and March 1958. Although the Asian flu pandemic was nowhere near as devastating as the 1918 pandemic, more than 1,000,000 people died worldwide, including almost 70,000 in the United States. The emergent development of a vaccine against the H2N2 virus and the availability of antibiotics to treat secondary infections were thought to have significantly limited the spread and mortality of the pandemic. But the sudden, spontaneous appearance of a brand new influenza virus derived from a combination of bird and human virus strains suggested a possible origin for the 1918 influenza pandemic and potentially for new pandemic strains – and this sent shivers of apprehension through scientists and doctors around the globe.

Enhanced appreciation of the continuous evolution of the influenza virus did nothing to prevent two subsequent pandemics. In early 1968, a new flu virus was detected in Hong Kong, found to be an H3N2 virus which arose by reassortment, with two genes from the migratory water bird reservoir combined with six genes from the virus circulating at the time in humans.⁵² The first record of the outbreak in Hong Kong appeared on July 13, 1968. Despite the surveillance efforts of the Global Influenza Network, the London *Times* was actually the first source to sound the alarm about the new pandemic. This H3N2 virus was highly contagious: within 2 weeks of its emergence, more than 500,000 cases of influenza had been reported. By the end of July, the virus had spread through all of South-East Asia and by September, the Hong Kong flu had reached the Philippines, Australia, India, Europe and the Panama Canal Zone. That same month, the virus entered California, carried by returning Vietnam War troops, and it was widespread in the United States by December. Worldwide, 700,000 people died due to the H3N2 virus with 33,800 deaths in the US. It was the mildest flu pandemic in the twentieth century, likely because the Hong Kong virus differed from the 1957–58 Asian influenza virus by only the HA antigen; its impact was likely moderated by partial immunity due to prior N2 exposure. Improved medical care and more effective antibiotics for secondary bacterial infections were also available for those who became ill. The H3N2 virus that caused the 1968 pandemic is still in circulation today and is the most prevalent influenza A strain involved in causing seasonal influenza.

Early in the spring of 2009, a new H1N1 flu virus was first detected in influenza cases in Mexico, associated with strikingly high mortality rates in younger individuals. Assessment of what was found to be the H1N1(09) virus was a complex reassortment story. In the late 1990s, a series of reassortment events were recognized to have occurred between North American influenza viruses found in pigs, humans and birds. As a result, “triple reassortant North American swine influenza viruses” with genes from humans, North American pigs and birds had been detected in many parts of the world for around 10 years prior to the 2009 H1N1 flu. Then in 2004, reassortant influenza viruses with genes from North American and Eurasian pigs were found in samples collected from pigs in Hong Kong. Mixing of the “triple reassortant North American swine influenza viruses” with Eurasian swine viruses resulted in the 2009 H1N1 influenza virus, a new, previously unseen strain of influenza which involved genes from at least four different flu viruses: North American swine influenza, North American avian influenza, human influenza A and Eurasian swine influenza viruses.⁵³ Initially, the epidemic was called the swine flu because all the different gene segments of the virus could be traced back to influenza viruses found in pigs. Once again, the vaccine prepared for the seasonal flu offered no protection and children were found to have no pre-existing immunity to the new strain. Again, a major pandemic was predicted. The H1N1(09) flu spread rapidly across the United States, to Europe, and eventually worldwide. In June, the WHO declared the outbreak to be a pandemic, the first in 41 years; ultimately, 74 countries were affected. New vaccines were emergently developed and these became available beginning in the early fall. By November 2009, 48 US states had reported cases of H1N1(09), mostly in young people. That same month, over 61 million vaccine doses were ready, just as reports of flu activity began to decline in parts of the country. Eventually, 80 million Americans were vaccinated against the 2009 strain of H1N1 and although belated, this may have minimized the impact of the illness. Globally, there were estimated to be more than 500,000 H1N1(09) related deaths, 80% in people younger than 65 years of age. The WHO declared the global H1N1 flu pandemic over on August 10, 2010.

The Vaccine

The WHO has been making annual recommendations for which viral strains to include in development of their annual vaccine since 1973, and from 1998 onwards, these have been made twice a year, for the Northern and Southern Hemisphere flu seasons. The WHO influenza network, now known as the Global Influenza Surveillance and Response System (GISRS) has grown large and complex from its origin in 1947, with 143 institutions in 113 Member States, six Collaborating Centers and four Essential Regulatory Laboratories. GISRS monitors trends in circulating influenza strains year-round, collecting genetic data and identifying new mutations. The data are provided remotely by National Influenza Centers (NICs) of the GISRS and other national influenza reference laboratories collaborating actively with GISRS, or are uploaded from WHO regional databases.

Since 1997, the system has used a global web-based tool called FluNet for influenza virological surveillance. The virological data entered into FluNet include the number of influenza viruses detected by subtype, critical for tracking the movement of viruses globally and interpreting epidemiological data. The data at country level are publicly available and updated weekly, as tables, maps and graphs. Each year, the annual flu vaccine combines antibodies against the viral strains which predominated in epidemiologic surveillance during the last year plus the three viral strains circulating most commonly in humans: influenza A (H1N1), (H3N2) and the influenza B virus; plus the three prominent subtypes of avian influenza A viruses known to infect both birds and people: H5, H7 and H9. However, intricate international reassortment events like those described for the H1N1(09) virus exemplify the complicated processes that the surveillance networks are trying to track. More than 250 million doses of influenza vaccine are produced annually against the WHO-recommended influenza strains.

The 1957, 1968 and 2009 flu pandemics were not detected in advance and the prepared vaccines offered no protection, suggesting that the surveillance program and the annual flu vaccine development process are essentially ineffective against new viral strains that develop suddenly by reassortment. Because there is a substantial time lag – estimated to be at least 6 months – related to vaccine manufacture time, a vaccine can even become obsolete because of new strains that emerge less rapidly, by spontaneous mutation. When a new, particularly virulent or widespread influenza strain appears – usually a brand new lineage developed by reassortment – a significant proportion of the population will have no resistance, so an additional specific vaccine has to be created emergently to prevent onset of a new pandemic. A recent analysis of flu vaccine effectiveness over 44 years indicates that the carefully composed, annual trivalent inactivated vaccine has an average efficacy of only 59% in adults, 18–65 years of age, with no demonstrated efficacy in adults 65 and older or in children below 17. The live attenuated flu vaccine given as a nasal spray showed 83% efficacy in children 6 months to 7 years old, but no studies supported its efficacy in older children or adults.⁵⁴ Just as originally reported back in the 1930s, the flu vaccine is and always has been only modestly effective against seasonal influenza. And against the constant background threat of a new highly infectious and highly virulent virus emerging suddenly by genetic reassortment, this extensive, surveillance process appears to be completely ineffective.

Finally – Identification of the 1918 Pandemic Flu Virus

An important piece of understanding the 1918 pandemic – specific identification of the virus which caused the pandemic – eluded investigators for more than 75 years, even as knowledge about the influenza virus increased and techniques for viral investigation advanced. In the years since the basic nucleotide units and the spiral helix structure of DNA were discovered, it was recognized that the order of the paired nucleotides contained all the information necessary for the hereditary and biochemical properties of life. Since that time, the ability to measure or infer these

sequences has become a major focus of biologic research, typified more recently by the Human Genome project. In 1977, Frederick Sanger developed the first technique for DNA sequencing, an early method to map the information coded in DNA.⁵⁵ This was followed by the development of the polymerase chain reaction technique, or PCR. First reported in 1983, PCR is a technique used to reproduce selected sections of DNA or RNA for analysis.⁵⁶ It allows isolation of fragments from genomic DNA or RNA by selective amplification of a specific region and can be applied to any nucleic acid sequence, even in samples containing only minute quantities of genetic material. Readers may be most familiar with it through its use in conviction of criminals based on recovery of very small DNA samples from crime scenes. It was not until 1995 that Jeffery Taubenberger, a molecular pathologist in the Armed Forces Institute of Pathology, hit upon the idea of using PCR to examine preserved lung tissue specimens from soldiers who died of the flu in 1918 as a way to reconstruct the genetic code of the virus which caused the influenza pandemic. Among the Institute's archived specimens, he found tiny cubes of preserved lung tissue from two soldiers who succumbed to the flu on the same day in 1918. PCR applied to microscopic sections of these specimens found the virus, but only in fragments. Subsequent PCR evaluation of lung tissue from an Inuit victim whose body had remained frozen in the permafrost from the time of her death during the pandemic allowed the researchers to sequence the entire genome and conclude that the influenza virus was an H1N1 avian virus.⁵⁷ Other researchers used the genome to reconstruct the 1918 H1N1 pandemic strain and test it in mice. All the mice infected with the reconstructed 1918 virus died, while all those exposed to a control strain survived. At autopsy, the researchers found severe inflammation in the lungs and bronchial passages, findings very similar to those in people who died of the 1918 virus. In a separate experiment, the reconstructed 1918 virus was found to be at least 100 times as lethal as an engineered virus that contained only five of the 1918 genes plus three genes from a control H1N1 strain. Subsequent testing in ferrets and monkeys showed similar high virulence for the recovered 1918 virus strain.⁵⁸ Based on all their findings, Taubenberger and his group theorized that the 1918 influenza virus jumped intact, directly from birds to humans.⁵⁹

DNA and RNA sequence analysis provides explicit information about the entire genome of an organism. Phylogenetic analysis compares DNA or RNA sequencing data from different organisms to construct a tree-like pattern that depicts the evolutionary relationships among the group and allows estimation of the time when a new viral mutation arose.^{60,61} Application of these phylogenetic techniques has answered critical questions about the 1918 pandemic influenza virus which persisted even after it had been completely sequenced and the virus recreated. What was the evolutionary origin of the virus? What were the origins of swine flu and of the typical, non-lethal H1N1 seasonal flu which emerged subsequently? Using a molecular clock model that explicitly allowed different evolutionary rates in different species, Michael Worobey and his team performed a complete phylogenetic analysis of full-length nucleotide sequences of all available influenza A viruses from humans, birds and pigs encoding the H1, H2 and H5 subtypes of HA and

the N1 subtype of NA from a repository of stored influenza A viruses in the Viral Genomes Resource at the National Center for Biotechnology Information at the NIH. Published in 2014, the findings of Worobey and his team indicate that genetic components of the H1 portion of the 1918 virus circulated in humans before 1907.⁶² The 1918 pandemic virus arose via reassortment between this pre-existing human influenza A H1 lineage and an avian strain, in a human or swine host. The pre-existing human H1 virus acquired avian N1 neuraminidase and internal protein genes. The resulting pandemic virus had seven RNA segments of avian origin plus one segment coding for HA from the pre-existing human virus strain. This novel reassorted strain explains both the virus' impressive ability to infect humans and the absence of immunity. The virus causing classic swine flu – the one discovered by Richard Shope in 1933 after the disease appeared historically in pigs at the time of the 1918 pandemic – appears to have descended directly from the human pandemic virus. The study's findings also suggest that the seasonal H1N1 virus developed by intra-subtype reassortment between the pandemic lineage and a co-circulating antigenically distinct H1 strain. Reassortment is clearly an important key to the pandemic potential of the influenza A virus.

Influenza Treatment

At the time of the 1918 pandemic, the only available treatment for influenza was supportive care. There were no antibiotics to treat secondary bacterial pneumonia, no ventilators to support pulmonary function and allow lung recovery, and no direct antiviral medications. Antibiotics began to appear in the 1930s and 1940s and are front-line treatment of bacterial pneumonia complicating influenza today. Artificial ventilation began with invention of the iron lung to support polio patients in 1929; this was replaced by positive pressure ventilators beginning in the early 1950s. Again, mechanical ventilation is widely used to support patients with respiratory failure in the context of severe influenza infection today. Finally, use of heart–lung bypass to allow the lungs to recover from overwhelming infection is an important element in treatment of individuals with lungs that have been critically compromised by influenza.

Perhaps most importantly, specific antiviral medications have been developed since the 1960s. These medications do not kill the virus directly, but rather attack at critical stages of the life cycle. Culture methods to identify the virus responsible for an illness have been available since the mid-1970s, followed by rapid influenza diagnostic tests (RIDT) which detect the influenza viral nucleoprotein antigen. Commercially available RIDTs can provide accurate results within 30 minutes or less and these are an important part of the contemporary management of influenza.⁶³

There are currently six licensed prescription influenza antiviral agents available in the United States: three are neuraminidase inhibitors that block the release of viral progeny in influenza A and B: the best known is oral oseltamivir phosphate, sold as Tamiflu; zanamivir is an inhaled drug marketed as Relenza; and intravenous peramivir is marketed as Rapivab. The fourth recommended drug is oral baloxavir

marboxil marketed as Xofluza – it is an endonuclease inhibitor that interferes with viral RNA transcription and blocks virus replication. The majority of currently circulating influenza viruses are susceptible to the neuraminidase inhibitor antiviral medications, oseltamivir (Tamiflu), zanamivir and peramivir. A second category of antiviral drugs is a class of medications known as adamantanes, which target the M2 ion channel protein of influenza A viruses: amantadine and rimantadine are only active against influenza A. There are high levels of resistance in the circulating influenza A virus population to the adamantanes so they are not currently recommended for treatment of influenza.

Clinical trials and observational studies show that early antiviral treatment shortens the duration of fever and illness symptoms and may reduce the risk of complications, with greatest benefits when started within 48 hours of influenza illness onset. Currently, the CDC specifically recommends initiation of a neuraminidase inhibitor treatment as early as possible for anyone with confirmed or suspected influenza who has severe, complicated, or progressive illness; who requires hospitalization; or who is at greater risk for influenza-related complications.⁶⁴ The combination of antibiotics to treat secondary bacterial infections, ascending levels of respiratory support and direct antiviral agents will hopefully decrease complications and mortality in the event of a future influenza pandemic.

Evidence of the excessive and potentially destructive immune response to severe influenza has raised the possibility of immunomodulatory therapy. A wide variety of agents have been assessed in animal and some human studies including corticosteroids, peroxisome proliferator-activated receptor agonists, shingosine-1-phosphate receptor 1 agonists, cyclooxygenase-2 inhibitors, anti-TNF factor therapy, intravenous immunoglobulin therapy, and statins.⁶⁵ High-dose steroids increase morbidity and mortality and are not recommended. Limited data suggest that combinations of antiviral and antibiotic agents may be useful. There are also limited data supporting the use of passive immune therapies like convalescent plasma and hyperimmune globulin.⁶⁶ Consistently effective targeting of the immune system in severe influenza is the subject of ongoing research efforts.

The Threat of Pandemic Avian Flu

When my mother explained the way Canada geese fly south for the winter, understanding of bird migration was of a relatively simple north–south transit pattern between known winter and summer nesting sites. More than 100 years of bird-ringing followed by satellite tracking in recent decades have revealed the true immense complexity of bird migration. GPS tracking shows that migration routes and schedules vary with each season based on multiple environmental conditions and individual bird and flock factors. Over time, the flyway concept emerged, defined as the system of migration paths that link resting and nesting sites and ecosystems for different birds in different countries and on different continents.⁶⁷ A single flyway is composed of many overlapping migration systems of individual bird populations and species, each with its own intrinsic habitat preferences and

migration strategies, and each subject to ongoing modification. Global flyway systems depicted on different map projections illustrate the enormous scope and complexity of bird migration and make obvious the potential for overlap of bird populations across continents. A polar projection like the one shown in Figure 4.4 highlights the fact that all the world's flyways converge over the Arctic. Given what we know about water birds as the natural reservoir of the influenza virus, this global aviation network provides a unique opportunity for reassortment between viral strains from different bird and animal populations with subsequent intercontinental disease spread along the migratory flyways.⁶⁸ In Figure 4.4, the arrows represent the direction of movement, and arrow width is proportional to the migration rate. Migration rates < 0.07 migration events per lineage per year are not shown. The area of each circle is proportional to the region's eigenvector centrality; larger circles indicate crucial nodes in the migration network.

This leads us to avian influenza. Influenza infection in domestic birds has been known to poultry farmers for centuries but was first recorded in Italy in 1878. The disease, originally known as Fowl Plague but now known colloquially as “bird flu,” causes intermittent massive outbreaks in poultry, including repeated major outbreaks in the United States, but before 1990, infections were sporadic and contained. In the 1990s, the world's poultry population exploded, reflecting the exponential growth in human population and the accompanying increased demand for animal protein. Poultry farmers responded with increasingly intensive poultry production methods including high-density farms and frequent flock movement plus breeding of a single, genetically homogeneous species, a perfect environment for contracting and spreading infection.

The virus causing Fowl Plague was identified as an influenza virus in 1955, but it was not until 1996 that the virus was isolated from a goose in China and found to be an H5N1 sublineage of influenza A. The potent flu virus now known as HP (for highly pathogenic) H5N1 was then recognized in Hong Kong in March of 1997, when it suddenly surfaced in chickens.⁶⁹ Flocks of infected birds acutely developed progressive difficulty breathing and then died, often within minutes; autopsies showed internal hemorrhage and severe necrosis of the lungs and other internal organs. Hong Kong scientists identified the virus as H5N1 but found it to be highly infectious, much more than the usual influenza virus. Then in May 1997, a 3-year-old boy was admitted to hospital in Hong Kong with fever and shortness of breath. Over the next several days, he developed respiratory failure and despite intensive support, progressive multi-organ failure led to death 7 days after hospitalization. Viral cultures in Hong Kong evaluated by multiple international laboratories confirmed infection with H5N1 – the first time an avian influenza virus had caused human disease. Fatal avian influenza in chickens recurred in the fall and in November, a 13-year-old girl presented with fever and pulmonary hemorrhage. Again, cultures were positive for HP H5N1 and again, despite intensive support, multiple organ failure developed and the patient died. When these cases were reported, there was immediate fear around the world that the H5N1 virus had mutated to be able to infect humans directly and therefore spread easily – that a new

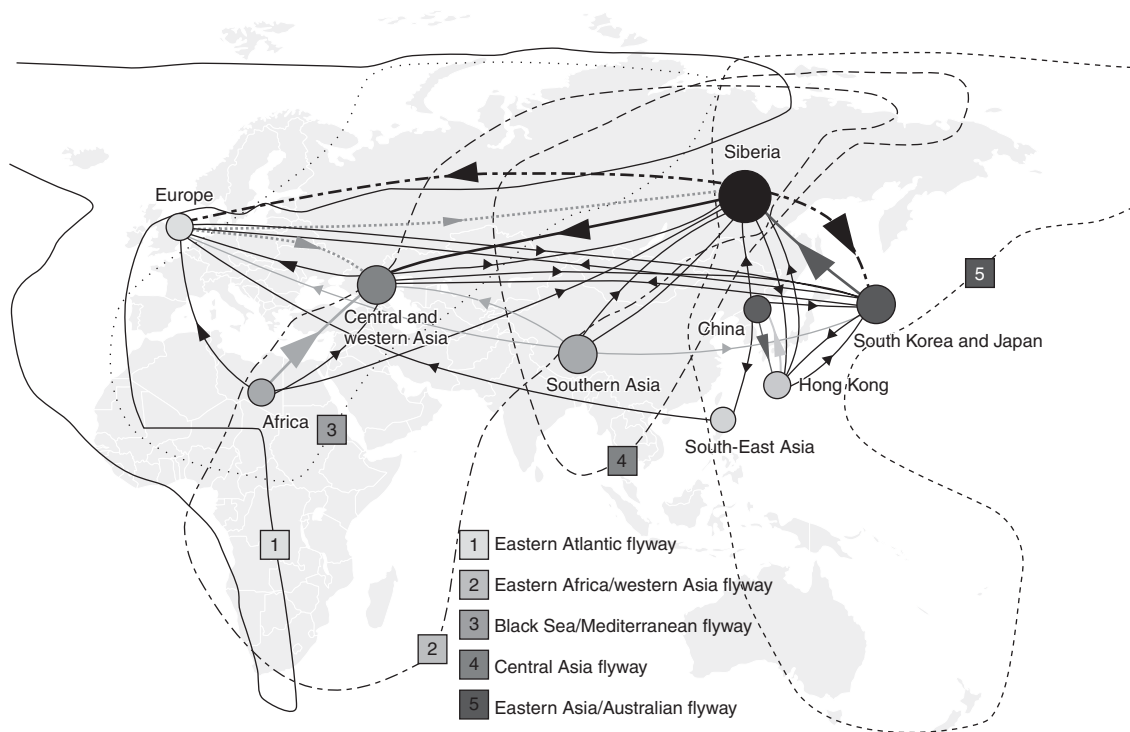


FIGURE 4.4 Global migration patterns of highly pathogenic avian influenza A (H5N1) viruses estimated from sequence data sampled during 1996–2012.

Source: Global and local persistence of influenza A(H5N1) virus. EID Journal 2014; 20(8). CDC.gov

and deadly pandemic was about to begin. The avian epidemic persisted in domestic birds, but by the end of December, there had been only 18 identified cases of H5N1 bird flu in people, of whom six died; one half of cases were in adolescents and children less than 13 years old. All occurred in individuals who had contact with live poultry in the days before they fell ill with evidence of very limited human-to-human transmission, only with close, sustained contact. Viral analysis of the avian and human cases showed > 99% correlation indicating disease had been caused by the same H5N1 strain and nucleotide sequencing suggested that the H5N1 strain was a reassortant from co-circulating avian influenza virus strains. Alarming, cultures of chickens in Hong Kong markets showed that almost 20% were infected with this virus. In response, the government ordered the slaughter of *all* poultry in Hong Kong, on farms and in markets: over the last three days of that December, 1.5 million chickens were killed. At the same time, importation of live chickens from mainland China was suspended. There were no further human cases of H5N1 in 1997 and virologists and infectious disease specialists in Hong Kong and all over the world breathed a sigh of relief.⁶⁹ After this alarming outbreak, the Hong Kong government instituted new infection control policies, but despite these efforts, the H5N1 virus was detected again in chickens and geese beginning in 1999 and in May 2001, clusters of chicken deaths from avian influenza occurred. The H5N1 virus was again isolated but shown to be a genetically different sublineage from the 1997 H5N1 isolate. There was a second territory-wide slaughter of poultry and the import of live birds was again suspended, the beginning of a recurrent pattern of culling and quarantine to attempt to prevent the spread of H5N1 outbreaks.

Despite these efforts at containment, HP H5N1 continued to spread to domestic poultry flocks, at first in Asia and then globally, ultimately involving multiple countries on four continents. China has been identified as the critical epicenter for the emergence of novel avian influenza viruses because of its traditional farming and marketing methods. In China, pigs and domestic waterfowl like chickens, geese and ducks are raised in close proximity to one another, and to the large numbers of humans that tend them. Wetlands used for rice production allow free-grazing migratory water birds to feed in the same areas year-round. This arrangement allows for frequent co-infection of pigs with both human and bird strains of the influenza virus and maximizes the potential for reassortment and the emergence of a novel lethal strain. And the Chinese people prefer to buy freshly killed birds, so there are “wet markets” – flash forward here to SARS and SARS-CoV-2 – where live birds and other animals from multiple sites are caged to be killed on the spot. Nowhere else on earth is the evolution of influenza viruses to include animal, avian and human strains facilitated to this extent. Studies in China confirm the existence of multiple H5N1 sublineages, expressing wide antigenic diversity. Once a novel avian influenza strain like H5N1 develops, migratory waterfowl are easily infected through shared water sources and can then carry the virus around the globe.⁷⁰

The HP H5N1 virus already has two of the characteristics necessary to cause a pandemic: it is a new microbial agent that infects humans and there is minimal or no population immunity. Lacking to this time is only easy and sustainable transmission

of the virus to humans and efficient human-to-human spread. Beginning in early 2004, there was a sudden increase in cases of H5N1 infection in people, traced to trade in live birds including wet markets and cockfighting. Human H5N1 cases grew to again involve four continents and more than 200 million birds have died or been culled in attempts to control the spread of H5N1 infection. The disease pattern in humans was similar to the original presentation in Hong Kong with a predilection for children and a mortality rate of ~50%. As of May 2019, the WHO has reported 861 human cases from 17 countries with 455 deaths, but case numbers have decreased dramatically over the last three years. The last case was reported from Nepal on April 30, 2019. Most cases occurred in people who had recent direct contact with H5N1-infected poultry, but there have been clusters of cases of human-to-human transmission, usually in families where there had been sustained close contact. Commenting on HP H5N1, Dr. Margaret Chan, then Director-General of WHO, stated:

The H5N1 virus is treacherous – we know that it can jump the species barrier to infect humans and that it is prone to mutation. Indeed, every case of human infection increases the probability that the virus will mutate. We don't know if or when the H5N1 virus might evolve into a pandemic strain that spreads easily among people, or what its lethality might be. We know only that a pandemic is possible, and that's why the world must prepare now for the very real threat of a global public-health emergency.⁷¹

Preparedness efforts against H5N1 have been extensive, with an H5N1 vaccine stockpiled for pandemic preparedness by the United States government to be used if the virus begins transmitting easily to humans and efficiently from person to person. But as we know, reassortment allows a new viral strain to emerge in a very short time and if the virus does develop easy and sustained human-to-human transmission, there will be no time for vaccine development or delivery. Epidemiologists have estimated that in a worst-case scenario, up to one billion people could die with HP H5N1 influenza within 6 months.

With the major decline in human HP H5N1 cases over the last two years, attention has shifted from H5N1 to H7N9 – H7N9 avian influenza A is a subtype that had been detected only in asymptomatic birds in the past. In March 2013, H7N9 presented for the first time in humans in China and since then, annual infections in both humans and birds have been observed. The disease is of concern because identified patients have become extremely ill with progressive severe respiratory illness after recent exposure to live poultry or poultry-contaminated environments, especially markets where live birds have been sold. This virus does not appear to transmit easily from person to person, and sustained human-to-human transmission has not been reported. During the fifth epidemic, from October 1, 2016 through September 30, 2017, the WHO reported 766 human infections with Asian H7N9 virus, making it the largest H7N9 epidemic to date. There were significant changes in the H7N9 virus detected during the fifth epidemic: infections in humans and

poultry were reported from most areas of China and all provinces bordering other countries, indicating extensive, ongoing geographic spread. Throughout the first four epidemics of Asian H7N9 infections, only low pathogenic avian influenza (LPAI) viruses were found, but during the fifth epidemic, mutations were detected identifying the emergence of highly pathogenic avian influenza (HPA1) viruses as well as viruses with reduced susceptibility to influenza antiviral medications. Furthermore, the fifth-epidemic viruses diverged genetically into two separate lineages, with one lineage emerging as significantly antigenically different compared with those from earlier epidemics.⁷² Because of its pandemic potential, candidate vaccine viruses were produced in 2013 to make vaccines against circulating Asian H7N9 viruses; at this time, the CDC is working with partners to enhance surveillance for Asian H7N9 viruses in humans and poultry, to improve laboratory capability to detect and characterize the viruses, and to develop, test and distribute new candidate vaccine viruses that could be used for rapid vaccine production if needed. Rare H7N9 cases have been reported outside of mainland China, most in people who had traveled to mainland China. The Chinese government is working to minimize Asian H7N9 spread by promoting large-scale poultry farming and centralized slaughtering, improving poultry product handling, routinely closing, cleaning, and disinfecting live poultry markets, and enhancing surveillance for influenza-like illness. H7N9 viruses have not been detected as yet in people or birds in the United States.

The genetic changes causing enhanced virulence observed during the fifth epidemic led to the WHO decision to classify Asian H7N9 as the virus with the highest potential pandemic risk among all viruses evaluated using their Influenza Risk Assessment Tool.⁷² In response, Chinese scientists developed a new H7N9 vaccine for chickens which was first used in September 2017. There has been a major decrease in H7N9 cases since then, suggesting that the vaccine may be effective. In addition, a human vaccine to prevent H7N9 infection is in clinical trials in the United States. As of June 6, 2019, a total of 1568 laboratory-confirmed human infections with avian influenza A(H7N9) virus have been reported to WHO since early 2013. Among them, 33 cases – all from China – were infected with HP A(H7N9) virus, with mutations in the hemagglutinin gene indicating a change to high pathogenicity.⁷³ To date, there is no evidence of sustained human-to-human transmission of avian influenza A(H7N9) virus.

Canada Geese Again

In December 2014, the importance of migratory water birds emerged again when an epidemic of a new H5 virus strain, HP H5N2, appeared in domestic poultry in the United States, introduced via North American flyways.⁷⁴ This highly virulent strain was apparently created when migratory water birds from North America and Asia intermingled in eastern Russia. The birds carried the new virus strain over the pole with the first HP H5N2 infections documented in Canada geese in western Canada and the northern US states.⁷⁵ Despite extensive existing safety measures

to protect domestic bird flocks, the disease spread rapidly involving captive wild birds, free-ranging birds, backyard flocks, and commercial flocks in 21 American states. Ultimately, the virus resulted in the deaths of more than 42 million chickens and 7.5 million turkeys either by direct infection or by culling to prevent disease spread, before the epidemic ended in June 2015. The disease destroyed 10% of the country's egg-laying chicken population and 3% of its annual turkey production – an estimated \$3.3 billion dollar hit to the US economy in 2015. There have been no human cases of H5N2 influenza, but this new and serious epidemic in domestic poultry reminds us that the capacity for rapid mutation, which is the hallmark of the influenza virus, means that the potential to cause new human or animal disease is always present and that migratory water birds are always available for rapid transport and dissemination.

Looking Back :: Moving Forward

Virtually unknown in 1900, viruses have since caused an ongoing series of terrifying pandemic disease, beginning with the 1918 global influenza pandemic. Unravelling the story of the influenza virus was a nearly century-long voyage of discovery which included development of advanced bio-imaging techniques, invention of molecular biology, major advances in microbiology and pharmacology, an increasingly sophisticated understanding of immunology, unravelling of the structure of DNA, transformation of clinical genetics and integration of human and animal biology, with collaboration of scientists from all those disciplines from all over the world. It is essentially the story of the emergence of modern science and modern medicine. It is now established that when human, avian and/or other influenza animal host viruses coexist in a single cell, an infinitesimal killer virus can emerge in the time needed for a single viral replication cycle. It was molecular genetic work that identified this most important characteristic of the influenza virus: endless evolution by both spontaneous mutation and by genetic reassortment leading to continuous emergence of new, antigenically novel strains. Faced with an entirely new influenza virus, human hosts have limited or no resistance, so these emerging strains have high infectious potential. In addition, the influenza virus is airborne, so transmission from one individual to another is remarkably efficient. At the same time, migratory water birds were identified as permanent reservoirs for the influenza virus and their interaction and migration were recognized as an efficient international delivery system for new viral strains.

We know now that constant genetic mutations and multiple hosts ensure that the emergence of dangerous novel influenza strains is inevitable. Since confirmation that the 1918 pandemic was caused by the influenza virus in the 1940s, there has been an intense, long-standing focus on development of an effective vaccine. However, from the outset, the technique for vaccine development was fraught with problems – problems that are intrinsic to the characteristics of the virus itself and to historic techniques of vaccine production. Based on success with previous development of vaccines against other viruses, the original influenza vaccines were

developed by growing the virus in fertilized chicken eggs, a technique which requires 6–8 months from start to finish. Given the success with development of smallpox and yellow fever vaccines, this was a very reasonable approach. However, with a constantly evolving pathogen, in the time required to develop a vaccine based on preventing the most prevalent strains circulating in the *previous* season, an entirely new and dangerous strain can easily emerge. In fact, the pandemics of 1957, 1968 and 2009 confirm that this is not a theoretical concern. A new method based on mammalian cell culture technology has been in limited use since 2012, but this cuts only 5–6 weeks off the production time. In addition, the FDA requires evaluation of the safety and efficacy of each new vaccine through clinical trials in an appropriate target population – the cost and time required for these trials is also significant. At the same time, the WHO's GISRS is now a massive, enormously complex and costly process, involving more than 140 institutions in 100 Member States with multiple Collaborating Centers and Regulatory Laboratories using a global web-based tool for year-round influenza virologic surveillance. The intricate international reassortment events described for the H1N1(09) pandemic virus exemplify the complicated processes that the surveillance networks tried – and failed – to track. The vaccine developed to prevent infection with the pre-identified 2009 seasonal strains was completely ineffective against the pandemic virus which originated when three strains of influenza merged by antigenic shift, reassortment, and recombination, with pigs as the mixing vessel. More than 250 million doses of influenza vaccine are produced annually against the WHO-recommended influenza strains; a 2013 World Health Organization analysis pegged each manufacturers' cost of refreshing the annual vaccine at \$5–18 million per year with return of an estimated three billion dollars of profit for the pharmaceutical industry per year.⁷⁶ All this time, effort and money produces an inadequate product, only effective in an average 59% of subjects. A new approach is urgently needed.

While knowledge of the influenza virus was increasing and recognition and management of influenza epidemics was improving, global vulnerability to an infectious pathogen also increased with growing world population density, rapid and frequent global trade and travel, chaotic urbanization, recurrent wars, substandard living conditions, and the effects of global warming. Complete understanding of the emergence of influenza viruses, their variable pathogenicity and their capacity for continuous evolution remains an ongoing effort which must be integrated into the context of ever-increasing global risk. The challenge for science and medicine going forward is rapid detection and elimination of new life-threatening microbes in an increasingly vulnerable world.

Moving forward, a new approach to influenza vaccine development is clearly indicated. In response to this pressure, there have been efforts to develop a universal flu vaccine that would convey durable cross-protective immunity against diverse virus strains dating back many years. Studies in animal models show that using relatively invariant parts of the virus can induce immunity with the most promising approaches based on antibodies specific for the relatively conserved ectodomain of matrix protein 2 and the infra-subunit region of hemagglutinin.⁷⁷ Multiple teams

have taken up the challenge of developing a safe and effective universal influenza vaccine, using a wide variety of strategies including vaccine-induced antibodies against the HA stem, blockage of interferon evasion genes with a constructed virus, and antibodies that bind to the influenza virus and recruit T cells to destroy infected cells.^{78–83}

Two universal vaccines are in clinical trials: on February 12, 2019, a team from the University of Wisconsin announced preliminary results from a successful Phase II trial of its nasal flu vaccine M2SR (Redee Flu). The vaccine is based on a novel approach to prevent replication of the influenza virus in humans, by introducing a live virus that cannot replicate but triggers a robust immune response ensuring broad protection.⁸⁴ The results of Phase III trials are pending.

The novel influenza vaccine MVA-NP+M1 is designed to boost cross-reactive T-cell responses to internal antigens of the influenza A virus that are conserved across all subtypes, providing protection against both influenza disease and virus shedding against all influenza A viruses.⁸⁵ Following a Phase I clinical study that demonstrated vaccine safety and immunogenicity, a Phase II trial is currently testing the vaccine's efficacy in 862 people aged 65 and older, with study end projected to be October 2019. MVA-NP+M1 is the furthest along of all the new universal vaccines in terms of human testing but even if a vaccine proves to be safe and effective in Phase III trials, it will be another 5–7 years before it becomes available.

A novel approach to efficient vaccine development is the synthetic generation of influenza vaccine using recombinant DNA techniques to generate HA and NA gene sequences as a synthetic candidate virus on a standard vaccine backbone. This virus template would allow instantaneous exchange of identified sequence data from a pandemic strain with local gene synthesis. Using this technique, a vaccine tailored specifically to address a new pandemic strain could be developed almost instantaneously and produced locally, eliminating many of the time-consuming steps in the traditional process. Gene synthesis by this cell-free, enzymatic technique has enormous theoretical appeal, although there are substantial technical and regulatory hurdles to be addressed. The FDA has approved one vaccine developed using recombinant DNA, but it is not yet utilized for routine immunization.^{86,87}

The influenza A virus has proven to be a master of evolution, constantly adapting to new environments and evading immune responses and attempts at prevention with vaccines. For the last hundred years, novel antigenic influenza variants have been responsible for annual seasonal flu epidemics and for four devastating global pandemics. In the early years of the twenty-first century after the HP H5N1 virus first presented in people, many public health experts feared the imminent development of efficient person-to-person transmission leading to a worldwide H5N1 pandemic with very high mortality. That has not happened – not yet, at least – and now concern is focused on yet another influenza virus with what is thought to be even greater pandemic potential, H7N9. Intervening pandemics with Ebola, Zika, and SARS-CoV2 have shifted attention away from influenza. However, according to Dr. José Esparza, president of the Global Virus Network, “Most pandemics can at least theoretically be controlled with well-established measures of case isolation,

contact quarantine and good infection control in hospitals. The one major exception is pandemic influenza – public health measures and pharmaceutical interventions have only limited effectiveness and pandemic vaccines take months to develop and deliver.”⁸⁸ A contemporary, mathematically based simulation estimates that a new lethal influenza strain like the one that caused the 1918 flu could kill 33 million people in 6 months.⁸⁹ The Bill & Melinda Gates Foundation and the Page Family have provided strong support for research into development of a universal flu vaccine by launching the “Universal Influenza Vaccine Development Grand Challenge” during the centenary year of the 1918 flu pandemic. The challenge offers up to 2 million dollars to fund research designed to identify “novel, transformative concepts that will lead to development of universal influenza vaccines offering protection from all subtypes of circulating and emerging (drifted and shifted) Influenza A subtype viruses and Influenza B lineage viruses for at least three to five years”.⁹⁰

Meanwhile, the 2017–2018 US seasonal flu was more widespread and more severe than any year since the 2009 swine flu pandemic, with more hospitalizations than in the previous 5 years and 186 deaths in children, above the previous high reported during the 2012–2013 season. The 2018–2019 season was less severe with only 116 pediatric deaths.⁹¹ But already in 2019–2020, at least 250,000 Americans have been hospitalized and 14,000 people have died due to influenza, including 105 flu-related deaths among children, a higher total at this point of the year (February 2020) than any season in the past decade. This year’s vaccine effectiveness against any flu virus was 45%, better than any vaccine since 2015–2016, CDC data shows.⁹² But the next influenza season begins in 7 months and a lethal new influenza strain emerging in China is only a transpolar flight away ...

I still look up in wonder when I hear the call of Canada geese overhead. I think I always will. But some component of the awe I feel now includes comprehension of the critical role that migratory water birds play as the reservoir of the amazing and terrifying influenza virus.

HISTORIC PERSPECTIVE: INFLUENZA AND THE PUBLIC HEALTH MOVEMENT

Influenza struck North America in late 1918 and created an epidemic memorialized for its high mortality rate and seeming predilection for healthy young adults. The North American outbreak was part of the global pandemic that affected the entire world, killing 21 million worldwide and more than half a million in the United States. Some of its reach can be attributed to the troop movements associated with World War I. The effectiveness of the public health movement rallied in opposition to the epidemic also owes a great debt to the infrastructure attached to the war; this produced the framework – especially the tight links between

the government and public health – upon which modern US public health still rests. This historic perspective will examine responses to influenza across the United States and demonstrate its resilience in current public health architecture.

The fall of 1918 saw the American public health service hard at work promoting worker welfare in areas essential to the war effort, including health care of military personnel, an aggressive campaign against venereal disease, and improved working conditions and health promotion for industrial workers participating in manufacturing. Those efforts might have distracted the Surgeon General and the rest of the public health infrastructure from the early flu reports surfacing across the north-east in the spring and summer. But by October, which saw the deaths of 4500 in Philadelphia and 2300 in Chicago in a single week, the effort to combat the flu was in full swing. That meant coordinating reports from all over the country on mortality rates, mass public education, and the appointment of state influenza directors to distribute doctors and nurses to the most severely affected areas. The volunteer medical corps was also raided to provide additional physicians and nurses to join the influenza combat ranks. Their salaries became part of the government payroll during the epidemic, and they were deemed vital to the nation's health. These efforts were fueled by a one million dollar appropriation by Congress. Tremendous power was also granted to the Attorney General, including the right to restrict fundamental Constitutional rights, like the freedom of assembly. The Attorney General exercised this right on October 5, 1918 to close all areas of public assembly. His order was carried out by local public health departments, and across the country schools, theaters, churches, and restaurants closed. Anti-spitting laws originally designed to curb tuberculosis were enforced, and in many areas, new laws were written to order the wearing of masks in public.

These prevention efforts proved insignificant in light of the vast number of new and critically ill influenza cases. The public health service responded by appointing new officers specifically to address the epidemic, creating a network of emergency hospitals, hiring thousands of physicians to staff these new facilities and beginning vaccine trials. When the number of new cases finally began to decline at the end of November, the public health service found itself in a new role: no longer devoted to prevention and treatment, it turned its attention to damage assessment. A team of interviewers began conducting door-to-door surveys across the nation, and their findings were analyzed by a PHS statistician. It was these findings that, despite the relatively small sample, showed the most vulnerable population to have been previously healthy 20–40-year-olds and the baseline mortality rate to have been at least 55,000.⁹³ All these efforts reflected the need for a stronger federal public health authority, because the PHS was left scrambling at the beginning of the epidemic to

hire staff and establish the necessary infrastructure to educate about the disease, disseminate information about how it was transmitted, reduce transmission rates, treat the sick, and assess national and regional morbidity and mortality. Most of the PHS's success was due to local and regional efforts, and it is both by examining those and dividing the effort by race that it becomes clear that this was not yet a truly national public health service.

The American Red Cross (ARC) was perhaps the most effective of the groups mobilized in the fight against influenza, and it worked with the PHS to provide treatment and propagate information about the means of transmission. Its standing was bolstered by its links to the government, which included reporting directly to Congress and its status as the official organization designated to respond to disasters and carry out the US government's responsibilities under the Geneva Convention. The ARC operated through a network of regional and local offices, and these expanded considerably during the course of World War I. President Wilson organized a board to control the Red Cross when the United States entered the war, and that board expanded the organization substantially, recruiting at least eight million female volunteers as well as reorganizing to include 14 regional divisions with 12,700 staff and 20 million members. Part of the ARC's mandate included hiring nurses, as well as recruiting female volunteers. It is worth noting that black women consistently faced rejection, both as nursing candidates and as volunteers. This racial divide would limit the opportunities for black women to serve overseas, as well as have significant repercussions for public health efforts, including those mobilized against influenza. The very African American women who were refused the chance to serve overseas were assigned to care for servicemen on military bases afflicted by the flu; other women also rejected as unsuitable, such as married women, joined their ranks. The white nurses who had previously held the gates of their profession closed against black women and kept their numbers restricted to those who were unmarried found they no longer had sufficient personnel to justify these decisions. Although it would take many more decades to end racial segregation in the ARC and the medical profession, the work of African American women in the influenza epidemic initiated a slow shift in nursing demographics. Even in the midst of the epidemic, however, white officials were reluctant to permit African American nurses to care for white civilian patients.⁹⁴ Ironically, racial segregation might have benefited African Americans when it came to influenza, because this is one of the factors to which their lower mortality rate during the epidemic has been attributed. Other factors include the poor conditions in African American neighborhoods that might have increased the number of cases in the spring influenza season and thus provided immunity during the deadlier fall outbreak, and inaccurate reporting of African

American flu mortality.⁹⁵ The lower morbidity and mortality rate among African Americans did nothing to erase racial medical theories that defined African Americans as biologically inferior and more prone to sickness, since it reinforced the idea that black and white people were constitutionally different in their responses to disease.⁹⁶ The long-term effects of this racialized medical thinking would be experienced at least through the end of the Tuskegee Syphilis study in 1972.

The ARC effort was nationally organized, but it was locally run. Regional and local offices were responsible for a significant effort to combat the flu, including provision of approximately \$2 million in supplies and equipment to hospitals, transportation of health care workers, supplies, and bodies, creation of institutions to care for patients and to feed and house those left homeless and orphaned by the disease, and recruitment of nurses and other volunteers to serve alongside PHS personnel.⁹⁷ As Moser Jones argues, however, the success of the ARC's efforts showed high regional variation that demonstrated the weaknesses inherent in a system dependent upon coordinating even a quasi-governmental organization with the governmental wing responsible for public health and the importance of cooperation on the ground among all acting agencies.⁹⁴ She contends that the regional variation in response efficacy reflected not just a disconnect between what the federal government and the ARC central authority deemed "the right way to respond," but also the centrality of a culture that valued volunteerism at the community level as an important aspect of citizenship.⁹⁸

The nation might have valued volunteerism, but the federal government viewed the inconsistent regional cooperation with central authority to be a significant weakness in the public health infrastructure. Federal efforts to promote public health had begun as early as 1798, when Congress passed a law authorizing the establishment of hospitals to care for sick and disabled seamen. It continued in 1871 when Congress created the position of Surgeon General, originally intended to head the Marine Health Service, and became more institutionally bound when Congress passed the National Quarantine Act in 1878, transferring the power of quarantine from states to the Marine Health Service, and when a federally funded laboratory was established on Staten Island to study communicable diseases in 1887. Eventually the three areas of federal responsibility for public health would be handled by the National Institutes of Health (established in 1930), the Centers for Disease Control (established in 1946), and the Federal Emergency Management Agency (established in 1979).⁹⁹ It was the influenza epidemic that prompted the first articulation of the need for a federally controlled and funded public health infrastructure that was resilient to regional variation. It took 60 years to fully realize that initial goal which has since expanded. FEMA and the CDC have the

federal power to quarantine, first granted during the 1918 influenza epidemic but not used since, although states and cities have exercised their right to quarantine as recently as the Ebola outbreak of 2014.¹⁰⁰

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5

POLIO

The Plague of Summer

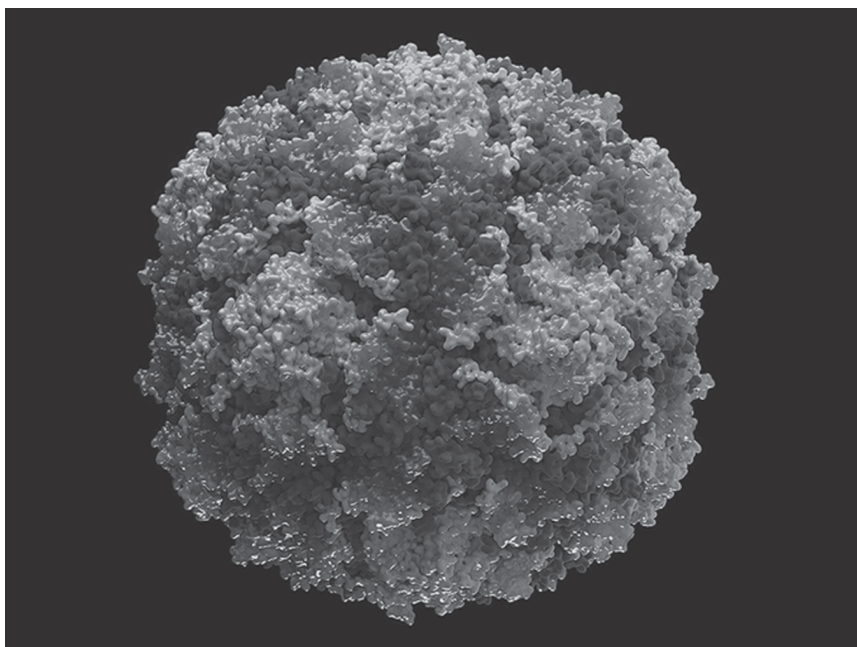


FIGURE 5.1 Electron micrograph of polio virus.

Source: cdc.gov

A POLIO STORY

Our family has its own polio story. I was only 5 so I don't remember the details myself, but it is part of family lore so I have heard it many, many times. Every time anyone mentioned polio, my mother told this story – and she always started the same way:

It was the October after Brian was born – Rae-Ellen was 5, Sally was 3 and the baby was 2 months. Rae-Ellen was always the healthy one, never sick and never tired. But early in the fall of first grade, she came home from school and fell asleep in the big armchair in the living room. When I went to wake her for dinner, her cheeks were bright red and she was very hot – burning up with fever, as her grandmother used to say. Her temperature was 104 degrees, almost as high as my little brother Sam's had been, back when he was so sick with mastoiditis and had to have surgery. She said her throat hurt and she wouldn't eat anything. I gave her a baby aspirin and a cool bath and then moved her into the bedroom downstairs, hoping her sister would not get sick too. In the night, she woke up crying and I found her shivering so hard her teeth were chattering. I gave her more aspirin, wrapped her up in a quilt and rocked her in the old chair we used to have by her crib when she was a baby. I couldn't remember the last time I had held her in my arms – with the new baby and Sally, Rae-Ellen was my "big girl." I held her tight and finally the shivering stopped – she was still glowing with fever, but she was asleep so I slid her back into bed.

In the morning, she seemed a little better – she even drank a little apple juice. Her dad didn't think we needed to call the doctor and he left for work. I was racing around trying to clean up the kitchen and feed the baby with Sally coloring at her little table when I heard Rae-Ellen crying. I could see right away she was worse, with spasms of shaking that racked her whole body before subsiding, only to start again. I tried to get her to take more aspirin but she wouldn't even try to swallow. She said her throat hurt and her ears and her neck. I remember that moment so well – my heart just stopped because I knew neck pain was a sign of polio. We had had a few polio cases in our neighborhood that summer and a little girl from our street was still in the hospital with it. My women's group at the church had a special meeting in July to go over the signs of polio and I remembered that neck pain was an important one. A new member who had moved to Edmonton from the states brought something called "The Polio Pledge" which we were all supposed to sign – with Brian born in August, I hadn't gotten around to signing it, but it was still thumbtacked to the bulletin board in the kitchen and sure enough, neck pain was right at the top of the list of things to watch for. I went straight to the phone and called the doctor's office.

It was late afternoon before Dr. Fraser arrived and by then, I was a wreck from worry. We had only been living in Edmonton for a year and I didn't know him well, but I tried to be calm, hanging up his coat and offering tea as I pointed the way to the bedroom. He headed straight down the hall, looking back over his shoulder to ask what was going on. As soon as I said, "She says her neck hurts," I saw him stiffen, just for a moment.

"What about her legs? Is she able to walk alright?" he asked. And I was so glad I could say that she had just walked to the bathroom by herself.

He carried his black bag into the bedroom and right away, I liked the way he was so cheerful and gentle with Rae-Ellen who at that moment was glowing like a light bulb.

"Well – what have we here? A pretty girl like you shouldn't be sick. Can you tell me what's bothering you?"

She looked very small in the bed but she spoke right up, just like she always did. "My throat hurts. And my neck and my ears."

"Can I take a look? I will need you to help me – can you do that?" Rae-Ellen gave a little nod and he took out a small flashlight and a tongue depressor that smelled like peppermint.

"Now you hold this special stick and open your mouth up wide – as wide you can. If you can open wide enough, I'll let you keep that special stick."

She did her best, opening her mouth and sticking her tongue out when he asked.

"Great job! Now you keep holding that stick while I look in your ears."

He used an instrument with a light to look in her ears and then felt her neck – I could see Rae-Ellen wince as he moved his fingers along her jaw. Then he asked her to lift up her head and look at her belly button – and she did with no problem.

"Let's see how strong you are – can you push my hands away?" He put his palms against the soles of her feet and I could see both legs straighten.

"Do you know something? You are a very brave little girl – can I have that stick back for a minute?" He took out his pen and drew a little face on one end of the stick, a little girl with big eyes and long straight hair. "There you go – a little portrait for a very good girl."

He was turning away when Rae-Ellen asked, "What is this stick for?"

The doctor looked surprised. "It's called a tongue depressor – I use it to push the tongue out of the way so I can see the back of the throat."

There was a pause. "You mean if someone doesn't open up their mouth you use this stick?"

"That's right – but you did such a good job by yourself that I could see perfectly without the stick. Now I'm going to talk to your mum for a few minutes and then I'll be back."

Out in the hall, I was rigid with fear but he said right away, "I know you're worried about polio but you don't need to be – there is nothing that suggests it. She has a bad strep throat and her neck is sore because all her lymph nodes are swollen and tender. I'm going to give her a shot of penicillin and she should start to feel better by tomorrow. If she doesn't, call the office and I'll come back out."

I was so relieved I just burst into tears. "She'll be okay?"

He patted my arm, "She's going to be fine. Thank goodness the polio season is pretty much over for this year."

And she was better by the next day and back to school by two days after that. That should have been the end of it, but all that long, cold winter, it seemed like she would have a "bad throat," as my mother called it, every few weeks. By the time spring finally came, I felt like I knew the doctor well and Rae-Ellen really liked him. Whenever he came to the house or we went to his office, she brought her special stick along. She even asked me to help her write a letter thanking him for taking care of her. But the bad throats kept coming back and eventually, he told us she needed to have her tonsils out. The operation was scheduled for July.

It was 1953 – the year of the biggest polio epidemic in Edmonton's history. Starting in May, our city newspaper – the *Edmonton Journal* – reported the number of new polio cases on the front page every day. It said this epidemic was the worst medical emergency Alberta had ever faced. Right in the Polio Pledge it said that children were at special risk for paralyzing polio after tonsillectomy, so Rae-Ellen's operation was cancelled. That summer was one of the hardest things I've ever experienced. It's impossible to describe the feelings of near panic and helplessness that I felt whenever any of our three had the slightest symptom. I knew polio could strike at any time, no matter how careful I was. One of our neighbor's children – a 7-year-old boy – came down with it in August and was in the special polio unit at the Royal Alexandra Hospital, paralyzed, on an iron lung. I had signed the Polio Pledge and I stuck with all the rules: all summer, I kept the children at home in the house or in our yard, away from other children and away from the community swimming pool where they usually took lessons – I never did learn to swim myself and I was determined that my children would learn – but not that summer. We didn't even go to church. Schools did not open until October when a heavy frost thankfully ended the epidemic. Rae-Ellen finally had her tonsils out in November and went right back to being the healthy one. But polio was never far from my mind until the vaccine came out in 1955 and all three of our children were vaccinated.

So that's the story. I only remember a few details myself and none have anything to do with polio. I remember waking up in the big bed in the downstairs

bedroom, all by myself. My grandmother – my mother’s mother – had severe rheumatoid arthritis and had been in a wheelchair since she was in her twenties. She lived with us in the summers and this was her bedroom on the main floor so she didn’t have to deal with the stairs. She had a real hospital bed that could go up and down and we loved playing with that, but I had never slept in the bed and had never been alone at night – as long as I could remember, my sister and I had shared a bedroom, so I was scared. I do remember the doctor coming. Strangely, I don’t remember the tongue depressor, but I do remember the shot. Of course, I had had shots before but none like this. The doctor took two thin glass cylinders from his bag and slid them together, one inside the other. Then he attached a long thin needle. He told me this was a special shot with medicine that would make my throat better – the shot would hurt but only for a minute and then I would start to feel better. He broke open a small bottle and filled the glass cylinder with liquid. There was a strong smell of alcohol and then a terrible burning pain in my bum. My mum held my hand and I didn’t cry. Afterwards, she put me on one of my grandmother’s heating pads and I fell asleep – and when I woke up, I already felt better.

I cannot remember that doctor’s face or writing him a letter. But I do remember how he made me feel special and that when I was sick, I knew he would make things right again. I am sure my experience with him is where my own interest in becoming a doctor began.

In his memoir about the 1953 polio epidemic in Edmonton, Alberta, Dr. Russell Taylor begins this way:

It was as if this vibrant, optimistic city had been smitten by a medieval plague; it engendered the same fear and helplessness. Arbitrary and insidious, it struck all ages and conditions, sweeping its victims from buoyant health to paralysis and death within a week. Like war and like plague, it left its mark on three generations. To those on the ground that year, there was no apparent pattern. It seemed that once the disease touched down, the whole prairie lit up like an old-fashioned switchboard.¹

Taylor was an internist who became director of an Isolation Ward turned Polio ICU at Edmonton’s Royal Alexandra Hospital in response to the epidemic. Between June 1953 and March 1954, the unit admitted 415 patients with polio – 25% of them required a respirator and 43 died. At the beginning, the unit had only one iron lung and the shortage of respirators was a desperate problem throughout the epidemic. The memoir is a gripping record of how medically challenging and emotionally agonizing it was to care for these young, desperately ill patients.

The “Polio Pledge” was developed in 1952 by the National Foundation for Infantile Paralysis, founded by FDR in 1938 to support polio research and provide care for polio victims; the Foundation eventually became the March of Dimes. In 1952, the Pledge was mailed to 35 million homes in the United States and delivered to every American school child.

The link between tonsillectomy and polio was first reported in 1929, and by the 1950s, the association had been confirmed in surveys from three continents.^{2,3} Analysis of extensive epidemiologic data revealed a potential causal relationship between removal of the tonsils and the onset of bulbar poliomyelitis – the most serious form, associated with paralysis of the respiratory muscles – within one month after surgery. It was theorized that if the throat was exposed to the polio virus in the early hours and days after surgery when the mucosal surface was still traumatized, the virus could pass directly into the central nervous system along exposed and traumatized nerve fibers. The summer pattern of polio infections was well known so the potential link with tonsillectomy led to recommendations to avoid elective tonsillectomy during the summer months and during polio outbreaks. This concern is essentially a thing of the past because the indications for tonsillectomy have resulted in a marked decrease in this procedure and polio vaccines have eliminated polio in developed countries. But 1952 was a different story: that was the year that the United States experienced the worst polio epidemic in the nation's history. Nearly 58,000 cases were reported and more than 21,000 people – mostly children and young adults – were left with some degree of paralysis.

There would be very few opportunities for my mother to tell her polio story today: at this point, almost no one outside of physicians involved in global health has ever seen a case of acute poliomyelitis. Most North American medical schools would have little opportunity to demonstrate conditions related specifically to polio.⁴ If the global polio eradication campaign is finally successful – now predicted for 2020 – it is tempting to think that polio will be completely relegated to the past. But the story of polio – a virus that traumatized the world for more than half a century – has much to teach us.

Polio: The Plague of Summer

This was how it began. Out of nowhere, young children were stricken with a strange disease that began with fever and ended with weakness and then paralysis of the legs. A *New York Times* report from August 4, 1899 tells the story of an epidemic of infantile paralysis in Poughkeepsie, NY with half the victims under 3 years of age.⁵ The treating physician was quoted as saying,

The disease is such an uncommon one that very little is known about it. I find that among specialists of disease in children, the remote cause is a mystery. The general symptom is a weakness of the muscles of the legs. Some cases show rapid improvement while others seem to do no better (over time). ... there is a danger (of permanent paralysis) leaving the muscles of the leg drawn up like a club foot.

The last sentence of the report carries an important clue, not much attended at the time “sufferers are found in families of rich and poor alike.”⁵

The Disease: A Chronology of Discovery

Infantile paralysis – the original name for poliomyelitis – was not unknown: Egyptian carved stone images from between 1580 and 1345 BC show a man with the typical withered calf muscles of a polio survivor and there are scattered references to paralyzed children thought to be polio victims in the Middle Ages and throughout the Renaissance. The disease was given its first clinical description in 1789 by the British physician Michael Underwood who called it “debility of the lower extremities.”⁶ In 1840, it was recognized as a unique condition by Jakob Heine who suggested it might be a contagious disease.⁷ The term poliomyelitis was coined by a German physician named Adolph Kussmaul in 1874, from the Greek *polio* for “gray” plus *myelos* for “marrow,” because the pathology showed inflammation of the gray matter in the anterior columns of the spinal cord.⁸

The first modern polio outbreaks occurred along with the increase in population density in cities during the Industrial Revolution. By the mid-1800s, small outbreaks of acute infantile paralysis, were being reported in Europe, distinguished by the young age of the victims and seasonal occurrence in the summer. But it was not until the end of the century that sporadic epidemics of the disease characterized by headache, fever, nausea, and stiff neck with weakness of the extremities and permanent paralysis in a significant percentage of victims began to occur in North America.⁹ The first well-recorded epidemic in the United States occurred in the summer of 1894 in Vermont. A young doctor named Christopher Caverly took care of all the victims and recorded the experience carefully. He described 123 recorded cases, 84 under 6 years of age, with permanent paralysis in 50 children and death in 18.¹⁰

This was one of many similar outbreaks in western Europe and North America reported at around this time, characterized by the same insidious onset, primarily in young children in the summer months and with the same serious residua of localized paralysis in up to half of symptomatic survivors. In 1907 and in 1911, after devastating polio epidemics in Sweden, Ivar Wickman published three important facts based on his careful observation of polio outbreaks in families in isolated rural communities. First, he confirmed the seasonal occurrence of the disease in late summer and early fall. More importantly, he reported that polio was spread directly from person to person and that there was subclinical infection, based on his observations in a small, isolated community that a new case in a family without polio often occurred after a visit from an asymptomatic individual whose family had an affected member. Finally, he identified the community school as the common source of the infections and deduced that apparently healthy children carried the disease home, where family members developed varied clinical presentations. He was the first to recognize that polio could be present in completely asymptomatic people and identified the importance of these cases in the spread of the disease.¹¹ In addition, if infected individuals could be asymptomatic, the actual rates of paralytic disease and mortality were far lower than in original descriptions of the disease. Nonetheless, each summer brought terror to the hearts of parents all over the developed world.

In the United States at the turn of the twentieth century, medical research was in its infancy with only a small number of scientists, most trained in Europe, engaged in original investigation. In 1901, the Rockefeller Institute for Medical Research opened, modeled along the lines of the Pasteur Institute in Paris, supporting investigators so they could work independently. Simon Flexner, the first medical director of the Institute, dedicated himself to research in infectious disease, specifically poliomyelitis. In 1908, Karl Landsteiner and Erwin Popper identified the causative agent for polio as a tiny filterable agent, invisible even with the strongest microscope – in other words, a virus (Figure 5.1).¹² In 1909 and again in 1913, Flexner and Paul Lewis published their research showing that this virus from human victims could be used to infect monkeys by swabbing the nasal mucosa and that the infection could be transmitted from one monkey to another, confirming that the disease was infectious and that the poliovirus was the infectious agent.¹³ Led by Flexner and the Rockefeller Institute, this was the beginning of the intense American medical involvement with polio.

During the summer of 1911, three Rockefeller clinicians performed a classic clinical study of a polio outbreak in New York city, describing the natural history of the disease in 71 hospitalized children and 90 outpatient cases.¹⁴ Their findings in families indicated that polio was highly contagious and confirmed that a significant number of those infected with the poliovirus had few if any symptoms. Their series emphasized that paralysis was not the presenting symptom of polio, but instead followed an initial stage characterized by non-specific symptoms of fever, lethargy, muscle pain, and headache. They reviewed multiple laboratory results trying to identify a defining diagnostic pattern, without success. Thirty-four cases were described in great detail including the history of the illness, the physical findings on presentation and the hospital course, day by day. These case descriptions illuminated the variety of presentations of infection with the poliovirus. The histories of 12 infants and children who died are described in heart-rending detail as hour by hour, progressive paralysis of the intercostal muscles and the diaphragm led to respiratory failure and death.

After this exhaustive review, the authors concluded:

At the present time there is no specific form of therapy by which the paralyzes in acute poliomyelitis may be prevented, or by means of which resolution of the inflammatory process and, consequently, return of function may be hastened. The problem of treatment, therefore, consists in preventing the spread of the disease to other persons, in applying general symptomatic procedures, and in attempting the restoration of muscular efficiency and the prevention of deformities.¹⁴

That same year, Carl Kling and colleagues reported that polio virus was present in the throat and intestinal tissues of people who died from polio. Soon afterwards they isolated virus from the intestines of patients suffering from acute polio, and importantly from family members who did not display any symptoms, confirming that

healthy carriers played an important role in spreading the disease.¹⁵ Unfortunately, this critically important finding did not gain much recognition at the time, at least among American researchers. Instead, led by Flexner, the Rockefeller researchers continued to investigate the disease using rhesus monkeys infected by swabbing the nose. In this animal model, infection by way of the nasal mucosa was shown to lead to clinical paralytic poliomyelitis with pathologic findings in the brain and spinal cord that were indistinguishable from those seen in patients with the paralytic form of polio. On this basis, Flexner became convinced that the virus gained direct access to the brain and central nervous system solely by way of the cribriform plate above the nose.¹⁵ Unfortunately, this incorrect focus on the polio virus as being “strictly neurotropic with entry to the body (only) by the nasal route” completely dominated polio research for the next 25 years so that well into the 1930s, there was very limited progress in understanding the true pathophysiology of the disease and therefore only limited progress in developing any approach to treatment or prevention.¹⁶

It was during this time that the germ theory of disease, first established in the 1890s, tragically intersected with the story of polio in the twentieth century. The culmination of the work of scientists dating back several centuries – recognition of how specific bacteria caused specific, distinct diseases – came simultaneously with understanding that ordinary actions including those of apparently healthy people were potential mechanisms for disease transmission. During the first part of the twentieth century, waterborne diseases like dysentery, cholera, and typhoid fever were the third leading cause of death in America. Major public health efforts then transformed the water supply using techniques of filtration and chlorination to purify the drinking water.¹⁷ Jersey City, New Jersey, was the first city in the United States to chlorinate its water in 1908, followed that same year by Chicago. In those cities that had introduced chlorination and water disinfecting techniques, death rates from waterborne diseases plummeted and within 10 years, more than 1000 American cities were chlorinating their water supply. By 1923 the typhoid death rate had dropped by more than 90% from the level a decade before.¹⁷ At the same time, municipal sanitation programs developed in the late nineteenth and early twentieth centuries and these were responsible for the design and construction of effective sewer systems.¹⁸ Similar efforts improved sanitation and clean water access in the developed countries of Europe plus Australia and New Zealand.

In the United States, these public health efforts were combined with extensive advertising campaigns to educate the American public in domestic hygiene practices, designed to exclude dirt and disease from the home, with specific efforts to prevent illness from spreading. Industry responded with antibacterial soaps, special cleaning powders and disposable paper towels to help prevent the spread of germs on cloth towels in public restrooms. The country became obsessed with domestic and bodily cleanliness as markers of health and social responsibility. There were even posters exhorting mothers to keep their homes clean, specifically to

protect their children from infantile paralysis. By World War I, proper hygiene was represented as an obligation that citizens owed their society.¹⁹

Against this backdrop of immaculate cleanliness and dramatically improved public health, polio was an unexpected and devastating invader. From the early 1900s onwards, small outbreaks occurred with increasing frequency all over North America including each of the Canadian provinces. Then, in the summer of 1916, there was a major polio epidemic in NY state. Beginning in June in Brooklyn, the disease ultimately spread throughout the state involving almost 30,000 symptomatic patients, 80% under the age of 5, before it ended. The *New York Times* covered the epidemic on its front page, reporting daily the number of new cases, their neighborhoods and the names of those who had died. The public reacted with panic and desperation:

But this knowledge availed doctors little in the scourge summer of 1916. Local newspapers reported that by the first of July, 350 New York children had been paralyzed by the disease and 75 of them had died. ... one hundred thirteen new cases were counted on July 5, and 133 followed on the sixth. Terrorized New Yorkers began freelancing solutions ... (they) cabled and wrote the Department of Health with all manner of things they were certain were causing the plague.

Tens of thousands of people decided to quit the city altogether. For families without the means to flee ... there was little to do but wait. In October ... the weather at last grew cool and New York City could begin to put the season of terror behind it. In the end, the doctors counted 27,000 cases of poliomyelitis around the country, 6,000 of them fatal. Nine thousand of the victims lived in the boroughs that made up New York City.²⁰

By the time it was over, the 1916 epidemic in New York city was reported to have caused paralysis in 2% of all children under two years of age.²¹

Although it was reported to the American public as beginning in immigrant Italians from the slums of NY city, polio contradicted the usual rule that infectious diseases flourish in the poorest living conditions – good hygiene, the health mantra of the time, was no protection against this dreaded disease. The physicians who cared for children with polio recognized that it actually occurred in homes with the best living conditions and in areas with the lowest population density. Scientists and physicians were baffled by this disease which seemed to strike the young in the healthiest environments.

It was not until the 1950s that a definitive explanation emerged: an unintended consequence of the national obsession with cleanliness was decreased exposure to infectious viruses like the poliovirus early in life when maternal antibodies would minimize symptoms but allow natural antibodies to develop. As understanding of immunity increased, the increasing frequency of polio outbreaks beginning in the early 1900s was attributed to the increasingly sanitary home environments resulting in limited contact with the poliovirus early in infancy. This theory was confirmed

when global antibody studies were carried out: in under-developed countries, most infants were found to have been exposed to the poliovirus very early in life without any symptoms of disease but with serologic evidence of immunity. By contrast, in industrialized countries, protective early immunizing infections were found to have occurred only in children living in crowded urban slums, while in affluent areas, evidence of exposure to the poliovirus did not occur until later in life when the paralytic form of the disease was more likely.²²

Back in the early 1900s, progress in understanding the disease and its spread remained slow. In her excellent book *Dirt and Disease: Polio Before FDR*, Naomi Rogers quotes one participant at a national conference in Washington, DC in 1916, as saying “polio is a disease the medical profession knows practically nothing about. ... that we are groping in the dark (to understand). ... (we) are doing all we can to ascertain what is its cause and how it is disseminated.”²³

Polio and FDR

Then in August 1921, Franklin D. Roosevelt (FDR), former secretary of the navy and a recent candidate for vice president, came down with polio and was left with paralysis of both legs. FDR symbolized many of the characteristics of an individual at high risk of this infection. He had been tutored at home until high school and therefore had experienced none of the usual childhood diseases as a young child because of lack of exposure. Subsequently, while at boarding school and then at Harvard when most of his peers were disease-free, he had scarlet fever, measles, mumps, and chronic sinus infections.²³ The week before he fell ill, he visited a Boy Scout camp where he was exposed to a large number of individuals in the age group known now to harbor the virus. He then engaged in a series of physically demanding activities which included extended running and swimming in ice cold water – histories of both excessive activity and “chilling” were reported in many cases of paralytic polio.²⁴ Although his age was not entirely typical, the age at polio diagnosis had been increasing and in 1921 when he fell ill, 30% of cases were in individuals over 10 years of age. His diagnosis made polio front page news all over the country.

Roosevelt never walked again without assistance. He tried every available therapy, most notably swimming and exercising in natural hot springs in Warm Springs, Georgia, and there is no doubt that his hard work there optimized his ultimate recovery. Despite his disability, Roosevelt campaigned for governor of NY state in 1928 and won. With the help of his family and staff, and the support of the press, he did his best to hide his inability to walk independently very skillfully, supporting himself with a cane on one side and the strong arm of his son or an aide on the other. With his powerful upper body for support, he used his shoulders to swing his legs – braced from the buttocks to the bottoms of his shoes – forward, shifting his weight from side to side, to simulate a normal walk. Eventually, he was able to use his right leg for support without a brace and to walk with a crutch and a cane, but he always had to be helped to his feet. Despite his efforts to disguise it



FIGURE 5.2 President Franklin D. Roosevelt in his wheelchair with his dog, Nala, and a young friend. This is a rare image revealing FDR's handicapped status.

Source: The National Archives. Franklin D. Roosevelt Library. 6/30/1941–6/30/1949. Archives.gov

and only rare use of a wheelchair in public as shown in Figure 5.2, his disability was obvious to all who saw him.²⁵

In 1929, the stock market crashed and the depression began. Many Americans blamed the Republican president, Herbert Hoover, so the field was wide open for an effective Democratic candidate like Roosevelt. Despite his significant handicap,

Roosevelt campaigned hard and in 1932, he was elected President of the United States. This had very important ramifications for polio and for medical research. Simply by living his life in the public eye, FDR challenged the prevailing stigma against people with disabilities. More specifically, as President, he brought polio directly into the mainstream, with a fundraising plan to keep Warm Springs, Georgia, going in the depths of the depression. He started by using a national advertising campaign to raise money. Local birthday balls were planned across the country to celebrate the president's birthday, with one dollar from each ticket going to the Warm Springs endowment fund.²⁶ The response was amazing, with more than 6000 parties held on the night of January 19, 1934; in the depths of the depression, Roosevelt received a check for over a million dollars! In subsequent years, with Warm Springs well taken care of, the plan shifted so that 70% of the income from the birthday balls would stay in local communities for care of polio victims. But with increasingly negative press from Republicans implying that the money raised was not being used appropriately, Roosevelt ended the fund-raising birthday balls and announced the founding of a nonpartisan "National Foundation for Infantile Paralysis" in 1938.²⁷

Until that time, medical research was funded largely by individual researchers using their own income or in rare research institutes established by wealthy philanthropists including the Rockefeller Institute, which had been researching polio without dramatic success since 1901. The National Foundation for Infantile Paralysis recruited Thomas Rivers from the Rockefeller to direct polio research and he outlined key basic priorities for conquering the disease, beginning with basic principles: understanding the pathology of polio, the portal of entry and the mode of human transmission – all still unknown despite decades of research. The Foundation established major virus laboratories at Yale, Johns Hopkins and the University of Michigan and the first coordinated research attack on polio began, funded entirely by public donations.²⁸

The National Foundation for Infantile Paralysis successfully broadened its fundraising to include movie collection boxes and celebrity endorsements plus the collection of dimes mailed directly to the White House. Ultimately, this "March of Dimes" became the name for the entire organization. Even as the United States entered World War II after Pearl Harbor, the organization maintained its revenue stream to sustain ongoing research and fund the care of polio victims. In the early 1950s, the National Foundation for Infantile Paralysis, supported entirely by public donations, spent 10 times more on polio research than the tax-supported National Institutes of Health.²⁹

The Disease: Epidemiology and Pathophysiology Defined

Over time and with the support of the Foundation, understanding of the clinical disease and its epidemiology progressed significantly. Originally, researchers who were unaware of clinical observations of the disease worked under the assumption that all cases of poliovirus infection resulted in paralysis, reflecting the prevailing

hypothesis that the virus was neurotropic and passed directly into the nervous system from the nose. It was not until 1941 that research by Albert Sabin and his colleague Robert Ward, funded entirely by the National Foundation for Infantile Paralysis, definitively confirmed that the poliovirus enters the body through the mouth and subsequently the gastrointestinal tract.⁴⁶ The primary site of virus multiplication was shown to be the mucosal lining of the mouth and GI tract with drainage into the related lymphatic systems and then the blood. In most patients, there was brief transient viremia after which the patient recovered. In a very small subset, the virus entered the central nervous system, either directly through spinal axons or indirectly through the blood, and infected the anterior horn cells of the spinal column and/or motor neurons in the bulbar portion of the brainstem, resulting in the classic flaccid paralysis of poliomyelitis. Antibodies to the virus were present early after infection in lab animals and in patients.

By analyzing New York sewage at a time when paralytic polio was prevalent, Melnick found the poliovirus in “huge quantities.”³⁰ Based on the case rate in the area from which the sewage came, he estimated a ratio of inapparent to paralytic infections of at least 100 to 1. During a polio epidemic in North Carolina, the same researchers found the number of age-specific subclinical infections per case to be 100–200:1.³¹ These findings confirmed the earlier family observations of Wickman and family physicians caring for paralytic polio cases who recognized that a significant number of those infected with the poliovirus have few or no symptoms. Based on studies like these, the true epidemiology and clinical pattern of poliovirus infection emerged:³²

- Humans were found to be the only known natural reservoir of poliovirus, although chimpanzees and Old World monkeys could be experimentally infected.
- Poliovirus infection typically peaks in the summer months in temperate climates with no seasonal pattern in tropical climates.
- Polioviruses spread through the oral–fecal route, when viruses from fecal matter are ingested, most often in contaminated water or food. The virus can also be transmitted directly from hand to mouth and from mouth to mouth.
- Poliovirus is highly infectious, with seroconversion rates among child contacts of nearly 100%, and greater than 90% among susceptible adults. Persons infected with poliovirus are most contagious from 7 to 10 days before and after the onset of symptoms, but poliovirus may be present in the stool for 3–6 weeks.

The response to poliovirus (PV) infection is highly variable with no symptoms at all in at least 90% of poliovirus infections; the ratio of inapparent to paralytic illness is at least 200:1. Infected persons without symptoms still shed virus in their stools and are able to transmit the virus to others. In 4–8% of cases, infection spreads to the bloodstream, causing a range of minor, non-specific symptoms, such as headache, sore throat, fever, and vomiting; patients with this pattern are completely recovered within a week.

In 1–2% of polio infections, non-paralytic aseptic meningitis with symptoms of stiffness of the neck and back and increased or abnormal neurologic sensation occurs. Typically these symptoms will last from 2 to 10 days, followed by complete recovery. Finally, paralytic poliomyelitis, the most serious clinical outcome, occurs in approximately 0.5% of all poliovirus infections, when the virus invades the central nervous system (CNS), causing inflammation and destruction of motor neurons leading to muscle weakness and paralysis.³²

The severity of paralytic polio depends largely on the site of motor neuron destruction, with highest morbidity and mortality resulting from respiratory or brain stem involvement. Weakness without sensory loss usually begins 1–10 days after initial symptoms and progresses for 2–3 days. Additional prodromal signs and symptoms can include changes in the reflexes and severe muscle aches and spasm in the limbs, neck or back. Even when the poliovirus reaches the CNS, the loss of motor skill may not be noticeable if less than 20% of the motor neurons in any area are destroyed. When more than 20% of the neurons needed for movement are affected, partial or total paralysis will occur. The extent and pattern of paralysis is random, but the lower extremities are affected with the greatest frequency. Generally, no further paralysis occurs after the temperature returns to normal. At no point do patients experience sensory losses or any changes in cognition. The illness progresses to flaccid paralysis with decreased deep tendon reflexes and reaches a plateau without change for days to weeks. Within 6–8 months, strength often begins to return. Many children and adults with paralytic poliomyelitis appear to recover completely and, in most, muscle function returns to some degree. Weakness or paralysis still present 12–24 months after onset is usually permanent.³²

Paralytic polio is classified into three types, depending on the level of involvement. *Spinal polio* is most common, accounting for ~80% of cases with manifest CNS involvement. It is characterized by asymmetric paralysis that most often involves the legs. *Bulbar polio* leads to weakness of muscles innervated by the cranial nerves and accounts for ~2% of cases. *Bulbospinal polio*, a combination of bulbar and spinal involvement, accounts for ~18% of paralytic polio cases. The overall death rate for paralytic polio is 2–5% among children and up to 15–30% for adults. Because bulbar polio can involve innervation of the muscles of respiration, the death rate is highest for bulbar and bulbospinal cases, as high as 75%.³²

Treatment and Recovery

Until 1927, there was no effective treatment for what was often temporary paralysis of the muscles that control breathing. Researchers at the Harvard School of Public Health devised a negative pressure respirator called an iron lung that could maintain respiration artificially until a polio patient could breathe independently again. A pump alternately lowered and then raised the pressure inside a rectangular, airtight metal cylinder, passively pulling air in and out of the lungs. Inside the tank respirator, the patient lay on a bed that could slide in and out of the cylinder as needed. The iron lung was the first mechanical respirator, the very first method

for temporary support of breathing. As muscle function recovered, patients could be weaned from the iron lung, but there are many well-described cases of polio patients with persistent paralysis of the muscles of respiration who lived in iron lungs for decades. To this day, the iron lung is virtually pathognomonic of polio.³³

In terms of residual paralysis, 10–40% of patients with paralytic polio reportedly recovered full muscle strength but 60–90% were left with variable paralysis, ranging from near total paralysis to isolated paralysis of individual muscles. Early muscle recovery reflected reduced inflammation of infected gray matter with improved function within weeks. Over time, remaining brainstem and spinal cord motor neurons developed new branches called axonal sprouts which could re-innervate orphaned muscle fibers, denervated by the acute infection, restoring the capacity to contract. Terminal sprouting could generate enlarged motor neuron units doing the work of multiple units: a single motor neuron that once controlled 200 muscle cells might control more than 800 cells. Finally, remaining muscle fibers with retained innervation hypertrophied and weaker muscles functioned at a higher than usual intensity, improving strength and function.³⁴

A critical factor in patients with paralytic polio was the preservation of normal sensation, which typically allowed control of bowel, bladder and sexual function and made active participation in muscle recovery efforts possible.

Historically, the formal practice of medical rehabilitation – the process of promoting and facilitating recovery from physical damage or clinical disease – dates back to the end of the nineteenth century when the concept of motor re-education was first proposed.³⁵ Physiotherapy, one of the key components of medical rehabilitation, first appeared in the English language in 1900 where it was described as “the use of natural forces such as light, heat, air, water and exercise in the treatment of disease”.³⁶ Gustav Zander, a Swedish physician, pioneered medico-mechanotherapy, the promotion of health and healing through the use of exercise machines that he designed in the late 1800s. In the early 1900s, two physicians trained by him established the Zander Room at the Massachusetts General Hospital, furnished with the earliest version of progressive resistance exercise equipment.³⁷ This progress in rehabilitation medicine was just in time for the influx of men injured in World War I and young patients paralyzed by polio. In the early stages of recovery from paralytic polio, therapy evolved to focus on light stretching of paralyzed muscles to prevent contracture, positioning and support of weakened muscles and joints, and hot packs to reduce painful muscle spasms. As muscle strength returned and muscle spasms resolved, physical therapists used manual muscle testing to grade the specific strength of involved muscles. They then applied selective resistance to facilitate movement and increase strength. Patients were trained to perform repetitive muscle re-education exercises based on the response to daily physiotherapy sessions. Patients learned to substitute for a paralyzed muscle by using surrounding, stronger muscles to perform the same function, guided by the results of repeated muscle function evaluation. As strength improved, progressive resistance exercises were used, often with water submersion. Over time, there was an increased emphasis on function including self-care and mobility with specific focus on gait training using

parallel bars and, when necessary, leg braces. Many of these techniques developed and evolved specifically as part of the effort to rehabilitate polio survivors, who included very young children.³⁵

It is impossible to overstate the critical role that Franklin Roosevelt played in the development of physical rehabilitation for polio patients. From his first realization that he was paralyzed and that recovery was going to be a long, long process, he was absolutely determined to walk again. To that end, he pursued all potential avenues of treatment. At that time, physical rehabilitation medicine was in its infancy and there was no recognized approach to optimizing the recovery of polio patients, so Roosevelt sought advice wherever he could find it. He had a physical therapist working with him daily from the early months of his recovery, stretching his muscles to prevent contractures and training him in what were eventually formalized as repetitive re-education exercises. He took daily baths in hot water mixed with salt, on the advice of his physician, Dr. Robert Lovett. Within two months, his upper body strength had recovered enough for him to sit upright – just barely – without support.³⁸ By one year after his acute illness, he could stand with full leg braces and some support and he was learning to walk with crutches after training at the Massachusetts General Hospital in the Zander medico-mechanotherapy laboratory under Lovett's guidance, with the most skilled physiotherapy available. Lovett recommended swimming in salt water and lying in the sun, things he had noticed seemed to help some of his other post-polio patients: FDR lay in the sun and swam in the ocean.³⁹ Then in the fall of 1924, he heard about Warm Springs, Georgia where a young man paralyzed by polio was reported to have recovered the ability to walk after swimming in the highly mineralized water from a nearby natural hot spring. From his first day at Warm Springs, FDR was convinced of the power of the hot springs. The high mineral content enhanced buoyancy so he was able to stand and exercise for hours without the exhaustion associated with trying to support himself on land. That first visit was the beginning of a major association with Warm Springs. He returned many times and stayed for months, making slow but steady progress.⁴⁰

Reports of his progress led to an influx of polio survivors from all over the world and Roosevelt welcomed them. He became actively involved with other patients, teaching them what he had learned about the benefits of aquatic exercise, testing and charting the strength of their muscle groups to measure progress, cheering them on.⁴¹ In April 1926, he bought the property with the goal of developing a comprehensive rehabilitation center for polio survivors. He hired national experts in polio care and designed a program focused on functional goals supported by swimming and exercise in the mineralized waters, adaptation of orthotic devices, massage and recreational therapy. He even sought the endorsement of the American Orthopedic Association. By 1940, the Roosevelt Warm Springs Institute supported 400 residents who profited from not just the programs provided but also by living in a completely accessible community, the first of its kind for disabled individuals. By his personal fund-raising efforts and then by establishing the National Foundation of Infantile Paralysis (NFIP),

Roosevelt insured the future of Warm Springs. The NFIP became actively involved in funding training and rehabilitation services while Warm Springs provided a model for successful physical rehabilitation and independent living that was applied to patients all over the world.

Despite his efforts to disguise his disability, Roosevelt's limitations were obvious to anyone who saw him. By living a public life with his disability simply part of who he was, FDR inspired people with disabilities of all kinds and helped to change the way individuals with physical handicaps were viewed. He became the champion for all people with disabilities and the de-facto founder of physical medicine and rehabilitation as a recognized medical discipline.⁴²

Early polio survivors – in fact, individuals who were disabled from any cause early in the first decades of the 1900s – had remarkably limited resources because progress in disability support and access was essentially non-existent at the time. Looking back, I realize that my grandmother was the first disabled person I ever met and she was very severely disabled. Her rheumatoid arthritis (RA) began in her late teens, but this was before 1920 when the only treatment was aspirin for pain. It was not until 1929 that RA was identified as an autoimmune disease and there was still no specific treatment. By the time she was 30, she already had multiple spontaneous joint fusions that severely limited her mobility. She was living on a farm outside a small town in Manitoba and had four young children. My mother remembered her cleaning the floor using one of her crutches to propel the mop. I have no idea how she managed to produce three meals a day, clean house and care for her children with the pain and limitation that the disease imposed.

I remember her as so tiny, her back severely curved by scoliosis. Her fingers were frozen in a closed position and the joints in her feet, ankles and knees were fused so that she could not walk without crutches. Despite all her problems, Sally and I absolutely adored her. She always had time for us – I remember her playing checkers with me: I would set up the board and then she would nudge her pieces forward with the frozen knuckle of her right index finger. She taught us how to bake, propped up on her crutches in one corner of the kitchen and directing us through recipes for butter tarts and raisin pie. I realize now that she could not have dressed herself – buttons and zippers would have been impossible. Yet every day we would find her sitting in her massive, “one-size-fits-all” wheelchair looking so pretty, wearing a blouse and skirt with a matching sweater. My mother must have helped her to get up and dress but I remember none of that.

I never thought of this at the time, but she was very close to being a prisoner on one floor of the house because she could not go up or down stairs herself without much time and effort and my mother could not carry her. When she did go out, she was carried down the stairs in that huge, unwieldy

chair by my father and my Uncle Sam. Amazingly, with no disabled access, she managed to travel by train across Canada, to live with each of her daughters and my Uncle Stan in succession. Her youngest son, my Uncle Sam, travelled with her and I can see now that she never could have managed without him as there was quite literally *no* wheelchair access to public transportation, schools, bathrooms or restaurants. These were the same problems faced by polio survivors at that time, struggling with braces and crutches and wheelchairs – or even worse, enormous iron lungs. The World Health Organization estimates that globally, there are more than 20 million people living with the sequelae of poliomyelitis. Reading the literature about polio survivors and how their leadership in the disability rights movement transformed the lives of millions of people is a true inspiration.

At Last – Progress in Polio Research

From 1938 forward, direction and support from the National Foundation for Infantile Paralysis resulted in dramatic progress in polio research after decades with limited results. At the Rockefeller Institute, Flexner's efforts to investigate the disease based on an animal model infected by way of the nasal mucosa were finally abandoned. There was important progress in polio research in 1931 when Australian researchers discovered there were two distinct serotypes of the polio virus while studying cross-immunity after experimental polio infection in monkeys. A third distinct type was identified subsequently in the United States. The three serotypes are named after the cases in which the type was first identified: type 1 (Brunhilde); type 2 (Lansing); type 3 (Leon).^{43,44} Type 1 was the serotype most often associated with paralyzing poliomyelitis.

Over the next decade, as both viral and immunologic research progressed, many different substrains of the poliomyelitis virus were identified, and in the late 1940s, a major effort was made to classify these immunologically. The work of multiple laboratories (including those of Albert Sabin and Jonas Salk) ultimately concluded that all poliovirus strains can be classified into three major groups based on the original described serotypes, each with distinctly different antigenic constitutions. Each serotype has a slightly different capsid protein that defines cellular receptor specificity and virus antigenicity.^{45,46} High antigenic variability characterizes strains, but the variability was always confined to the limits of the three serotypes when subsequently tested against panels of neutralizing monoclonal antibodies. This proved to be critical information for future vaccine development.

The primary site of virus multiplication was shown to be the mucosal lining of the mouth and GI tract with drainage into the related lymphatic systems and then the blood.⁴⁷ In a very small subset, the virus was shown to enter the CNS, either directly through spinal axons or indirectly through the blood, and infect the anterior horn cells of the spinal column and/or motor neurons in the bulbar portion of the brainstem, resulting in the classic flaccid paralysis of

poliomyelitis.⁴⁸ Importantly, regardless of the clinical picture, antibodies to the virus were shown to be present early after infection, first in laboratory animals and then in patients.⁴⁹

Polio Prevention: Development of Polio Vaccines

Expanded understanding of the virus and the pathogenesis of the disease occurred against a background of increasingly frequent polio epidemics beginning in 1940. The average age at diagnosis had increased each decade with 50% of cases over 10 years of age by 1942. The risk of paralysis and death also increased significantly as age at infection increased.⁹ The horrific nature of this disease that paralyzed children and the increasing number of victims led to enormous public pressure to find a solution. According to American historian William O' Neill, "Paralytic poliomyelitis was, if not the most serious, easily the most frightening public health problem of the postwar era."⁴⁶ Nearly 58,000 cases of polio were reported in the United States in 1952, with 3145 people dying and 21,269 left with some degree of paralysis. There was a rising tide of panic in the country with Americans naming polio as their greatest fear after nuclear attack. In response to this and to the increasing base of scientific knowledge, scientists became completely engaged with developing a vaccine. Against this backdrop, the March of Dimes sustained its successful fundraising, adding "poster children", polio survivors as models for what continued funding for care and research could achieve.

To this time, there had been only limited efforts at vaccine development because direct entry of the virus to the CNS was thought to preclude any role for circulating antibodies in blocking disease progression – and therefore any role for a vaccine. In addition, two disastrous vaccine attempts from the Rockefeller Institute in the mid-1930s had completely suppressed any enthusiasm for research in vaccine development.⁵¹ The demonstration of viremia and of circulating antibodies early in polio virus infection were both critical factors for vaccine development, as vaccine-induced antibodies could potentially block the virus when it was circulating in the blood and prevent invasion of the CNS.⁴⁹

Arising from the erroneous theory of direct CNS infection was a second incorrect doctrine bolstered by some failed experiments – that the polio virus could only grow in human nervous system tissue, a difficult process producing only a limited amount of virus. With recognition that the polio virus enters the body through the gastrointestinal (GI) tract, the Harvard team of Enders, Weller and Robbins decided to attempt to cultivate it on non-neural tissue. Their 1949 report that the polio virus can be reliably grown on cultures of various embryonic tissues dramatically changed the potential for vaccine development. The team received the Nobel Prize for medicine or physiology for this discovery in 1954.⁵² An accessible method to grow large amounts of polio virus galvanized vaccine development efforts and resulted in an historic rivalry between two young researchers, Jonas Salk and Albert Sabin, both funded by the National Foundation for Infantile Paralysis. This saga is described in detail in David Oshinsky's Pulitzer Prize-winning book.⁵³

Salk had worked on the development of a killed virus vaccine against influenza, so he used this approach. His laboratory at the University of Pittsburgh developed a technique for isolating pure polio virus and he found the virus grew well in monkey kidney cultures, a more accessible approach than the use of embryonic tissues. He selected three poliovirus strains, one of each serotype, inactivated them with formaldehyde and then tested the most virulent Type 1 strain safely in monkeys. He then tested a killed virus vaccine containing all three virus serotypes in institutionalized children at two facilities, a rehabilitation facility for polio survivors, and a public institution for children with IQ scores below 50. (At that time, experiments on children in institutions were considered acceptable if they could theoretically benefit from the intervention.) In both settings, the vaccine proved safe with no illnesses reported and high antibody responses to all three serotypes of polio virus persisting through months of follow-up.

In January 1953, Salk reported his killed virus vaccine results to the National Foundation's Committee on Immunization. There was discussion about a large field trial but no definitive plan emerged. Before Salk could even publish his work, news of the vaccine leaked into the lay press with a *Time* magazine article reporting "solid good news on the polio front."⁵⁴ Immediately, public demands for this vaccine accelerated in the context of the ongoing epidemic. Salk and the National Foundation were thrust into the awkward position of essentially denying Americans access to a vaccine developed by their own donations!

Salk's results were reported in the *Journal of the American Medical Association* and he and the National Foundation began immediate planning for a large polio vaccine trial.^{55,56} There was a major struggle over the design of the trial, but ultimately, there were two study arms with injection of second graders with real vaccine and observed controls in the first and third grades in 127 counties, and inoculation of all first, second and third graders, half with vaccine and half with placebo, in 84 counties. Combined, the trial included almost 1.8 million schoolchildren from the United States, Canada, and Finland in the largest public health experiment in history. Public attention was riveted on the vaccine trials which were extensively covered in the press. Two-thirds of all Americans(!) were reported to have donated money to the March of Dimes in 1954. The entire cost of the trial was supported by the March of Dimes, which also undertook the training of all of the trial personnel including 250,000 non-professional volunteers. Using March of Dimes dollars, a Vaccine Evaluation Center was opened at the University of Michigan. Despite negative commentaries from live virus vaccine advocates, the world's largest field trial began on April 26, 1954.

The trials ended in late spring of 1955, just before the beginning of the polio season. The results were announced at a press conference at the University of Michigan on April 12, 1955. The bottom line was clear: the vaccine was up to 80% effective in preventing paralytic poliomyelitis.⁵⁷ Edward R. Murrow, the father of broadcast news, announced the results from his show on location in the Vaccine Evaluation Center in Michigan that night, with Dr. Salk as his guest. When asked who owned the patent on the vaccine, Salk replied "Well, the people I would

say. There is no patent. Could you patent the sun?" Salk was a hero. As David Oshinsky writes,

Here, truly, was the people's vaccine, spearheaded by a charitable foundation, driven by the spirit of voluntarism, subsidized by millions of small contributions, aided by numerous scientists, tested by enthusiastic volunteers. Birthday balls, marching mothers, poster children – all had played a role. Developed in the public interest, this particular vaccine belonged to everybody.⁵⁸

The Salk vaccine was not perfect. Three doses were required to develop complete immunity and antibody titers waned over time. In addition, a large number of monkeys had to be sacrificed during vaccine development, approximately 1500 animals for every 1 million inactivated vaccine doses. Shortly after the vaccine was licensed, failure to completely inactivate the vaccine virus at one of the production laboratories resulted in 260 cases of polio and 10 deaths. Despite these problems, the response to the Salk vaccine program was very dramatic, as shown in Figure 5.3. In 1954, there were 30,000 cases of polio in the United States, compared with less than 1000 cases in 1960. The vaccine program was not without problems, but the dramatic results of the Salk vaccine were obvious.

Undeterred by the Salk vaccine's success, Albert Sabin continued research on a live virus vaccine at the Children's Hospital of Cincinnati. There were sound immunologic reasons to theoretically prefer a live virus vaccine, principally the fact that the antibody response was much more pronounced and long-lasting. While the Salk vaccine required three injections and subsequent boosters, a single oral dose of an attenuated live virus vaccine was projected to produce lifelong immunity. In

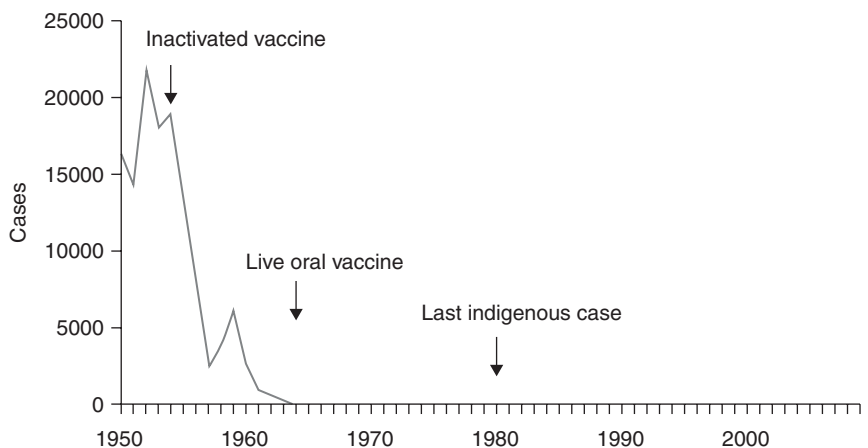


FIGURE 5.3 Poliomyelitis cases – United States 1950–2010. National Notifiable Disease Surveillance System, CDC.

addition, because those who ingested the oral vaccine would excrete the weakened virus in their stools, essentially infecting and immunizing many others in the population, the oral vaccine could theoretically eliminate susceptibility to the poliovirus completely. Finally, the oral, live attenuated virus vaccine produced local mucosal immunity via IgA induction in the gut, mimicking wild polio virus infection. By contrast, the injected, killed virus vaccine produces serum antibodies against the poliovirus and prevents neurovirulence but does not induce intestinal mucosal immunity.⁵⁹

Sabin carefully selected one strain of each poliovirus type that multiplied readily in the GI tract but demonstrated low neuro-virulence in monkeys and attenuated these by passing them through monkey tissue in rapid succession until a sufficiently weakened virus was produced – the same “passaging” technique used in developing the yellow fever vaccine. By 1954, he had developed three vaccines, one for each serotype, that did not produce paralysis when injected directly into the spinal column of monkeys, and in the winter of 1955, he tested these vaccines in 30 adult prisoners who had no poliovirus antibodies. All 30 developed antibodies and none became ill.⁶⁰ However, proceeding with further live-virus testing, especially in children, was blocked over concerns about reversion of the live but attenuated virus back to a more virulent state coupled with loss of public interest in light of the successful Salk vaccine campaign.

With no public interest in a trial in the United States, Sabin established a relationship with the University of Leningrad in 1956 and with the approval of the US State Department, a mass immunization program using the oral attenuated virus vaccines began in Russia, with a plan to immunize every Russian under the age of 20 – 77 million individuals. Within a year, the first results were available with a dramatic decline in paralytic polio cases, verified by the World Health Organization. In 1960, the Soviets – and subsequently Sabin himself – presented the results of their national vaccination campaign, reporting very significant progress towards the eradication of polio.⁶¹

Back in the United States, the steep decline in polio cases in response to the Salk vaccine led to a major decrease in public interest and research support. The National Foundation, now known as the March of Dimes, moved on to support research in birth defects and prematurity. With the success of the live-virus vaccines in Russia, Sabin conducted a new trial in the US in which the three monovalent vaccines were each given orally as a single dose in 200,000 individuals, primarily young children. The results led to trial development of the Sabin vaccine in the United States in 1960.^{62, 63} Then, before that trial had even been completed, the American Medical Association voted that the Salk vaccine be replaced by the Sabin oral vaccine as soon as it became available. Despite Salk's efforts to defend it, 1961 was the last year in which his killed-virus vaccine was used exclusively in this era to prevent polio. After 1964, the oral polio vaccine was developed in a trivalent formulation and over the next three decades, this live-virus vaccine was the vaccine of choice.

However, a serious consequence of the oral polio vaccine was described as early as 1962: rare cases of vaccine-associated acute paralytic polio caused by rapid

development of enhanced virulence of the attenuated virus strains in the vaccine.⁶⁴ Between 1961 and 1999, there were 1–2 cases of vaccine-associated paralytic polio (VAPP) per million primary immunizations with the oral polio vaccine.^{64,65} From 1980 through 1999, 162 cases of paralytic polio were reported in the United States; 154 (95%) of these cases proved to be VAPP, with the remaining six in persons who acquired wild-virus polio outside the United States. Some cases occurred in vaccine recipients and some in contacts of vaccine recipients. None of the vaccine recipients were known to be immunologically abnormal prior to vaccination. It became clear that the only way to eradicate polio completely in the United States was to eliminate live-virus immunizations by returning to the killed-virus vaccine and in 2000, the Salk killed-virus vaccine became the CDC's formal recommendation for immunization in the United States. With this change, all polio cases were eliminated in the United States.⁶⁶

The polio experience is unique among American epidemics and within medical history: the pace and direction of scientific progress were dictated by the public, fueled by media reports of dying and paralyzed children, with the work of scientists funded almost entirely by public donations, unhampered by government regulations. There is no doubt that short-term development of the killed-virus vaccine over long-term development of the live attenuated virus vaccine was driven by the intense public involvement. Today, development of a vaccine is a much more complex and expensive undertaking and can take 10–15 years from concept to public availability.

The Poliovirus

The intense focus on discovering a polio vaccine occurred at the same time that understanding of viruses in general exploded, based on advances in imaging, genetics and molecular biology. With these techniques, understanding of the poliovirus began to develop although complete characterization required decades of research.

The virus was first visualized by electron microscopy in 1952 and was seen to be very small, only 30 nanometers in diameter with striking icosahedral symmetry (Figure 5.1).⁶⁷ The genome is a single-stranded, positive-sense RNA, only 7500 nucleotides long. In 1981, the complete poliovirus genome was published simultaneously by two different groups.^{68,69} That same year, Rancaniello and Baltimore successfully cloned the poliovirus and showed that the clone produced infectious polio when introduced into cultured mammalian cells. The technique used to create this clone has been applied to the study of many other viruses.⁷⁰ Using x-ray crystallography, the three-dimensional structure of the poliovirus was demonstrated in 1985, the first human virus to be resolved in this way.⁷¹

The poliovirus was shown to infect human cells by binding to a specific receptor on the cell surface – a glycoprotein in the immunoglobulin superfamily of proteins. Labelled CD155, it was identified in 1989 and its recognition finally made it clear why the virus causes disease in such a small number of species – this receptor is found only on the cells of humans, higher primates and Old World monkeys.⁷²

After the poliovirus binds to CD155, it is taken up by endocytosis and viral replication begins. Within 4–6 hours, up to 10,000 polio virions are released by cell lysis, the primary viremia of polio infection.⁷³

The poliovirus genome has a very high mutation rate, among the fastest of all rapidly evolving RNA viruses, with both spontaneous point mutations and genetic recombination, just as we saw with the influenza virus.⁷⁴ Populations of polioviruses therefore always include multiple mutational variants, but unlike influenza, the genomic and phenotypic variability occurs only within the bounds of the three well-defined serotypes. This means that immunity to any virus within a serotype will confer immunity for all mutations in that serotype. Albert Sabin exploited this known variability of the poliovirus genome in selecting the three serotypes to be attenuated in his vaccine, deliberately selecting mutants with the capacity to replicate efficiently in the human GI tract but not in the CNS.⁷⁵ His goal was to create a strong immune response in the gut with very limited neuro-virulence, characteristics which were critical in the success of his vaccine.

By classification, the poliovirus is an Enterovirus in the family Picornaviridae, which includes foot and mouth disease, the rhinoviruses, hepatitis A and the Coxsackie viruses. It is currently classified as part of a distinct cluster, (Human) Enterovirus C which consists of the three poliovirus serotypes and 11 Coxsackie A viruses.⁷⁶ The poliovirus is structurally similar to other human enteroviruses. The poliovirus is hardy: it can survive for 4–6 months in cold water and in feces for months at 4°C and for years at –20°. However, it is inactivated by pasteurization, formaldehyde, hydrochloric acid and chlorine so there was actually little reason to worry about polio infection from swimming pools! It is resistant to lipid-soluble agents like bile and proteolytic enzymes of intestine hence its capacity to thrive in the GI tract.

Recent phylogenetic analysis suggests that the polio virus may have evolved from a C-cluster Coxsackie A virus ancestor through mutation resulting in replacement of the surface cellular receptor of the Coxsackie virus – intercellular adhesion molecule-1 – with CD155. C-cluster Coxsackie A viruses have the capacity to recombine with polio viruses to generate novel polio virus recombinants. Theoretically, this mechanism could contribute to the development of virulent vaccine-derived polio viruses.⁷⁷

Global Polio: The Challenge

Polio is often considered to be an American disease because polio crippled an American President, because much of the critical research occurred here, and because both vaccines were developed by American scientists. However, a parallel rise in disease outbreaks occurred in the first half of the twentieth century in developed countries all over the world including Canada, Europe (especially Denmark and Sweden), Australia, and New Zealand. The introduction of the two effective polio vaccines quickly and dramatically reduced the incidence of polio in each of these first world settings. Compared with the immediately pre-vaccine years

(1951–1955), the known global incidence of polio was reduced 700-fold by 1968. After the nationwide trial of Sabin’s oral polio vaccine in the USSR, the incidence there was also dramatically reduced.⁶¹

Belatedly, polio was also recognized as a major problem in developing countries, based on analysis of global statistics from the World Health Organization. Because the vast majority of individuals infected with polio have minimal if any symptoms, reports were based on “lameness surveys” that identified cases of acute flaccid paralysis with intact sensation.^{78,79} Given the limitations of this case definition and problems with identification and reporting in resource-limited situations, the real incidence is far greater. Estimated from pre-vaccine reports, the global incidence of polio cases is estimated to have been at least 600,000 individuals annually.^{9,80}

As the annual incidence of polio cases in the United States dropped exponentially following the introduction of the two polio vaccines, the wild poliovirus disappeared and was never identified in the US after the early 1970s.⁵⁴ This unexpected event raised the tantalizing possibility of global polio eradication. The poliovirus has a number of characteristics that theoretically make it a good candidate for eradication – humans are the only reservoir; although primates can be infected in a laboratory setting, there is no animal reservoir; there is an effective, inexpensive and easily administered oral vaccine; and previous mass vaccination campaigns to interrupt poliovirus transmission in Cuba and Brazil appeared to have been successful.⁵⁵ Beyond immunization, the attenuated poliovirus vaccine has another important advantage: children who take the oral vaccine excrete the weakened virus in their stools for up to 6 weeks, potentially infecting and immunizing multiple contacts in the population. Because the poliovirus needs a susceptible human population and a cycle of transmission for survival, mass vaccination could theoretically eliminate polio completely by exponentially enhancing the development of this herd immunity. The concept of herd immunity is based on the observation that if the number of pathogen-susceptible individuals is reduced to a sufficiently small number, then the pathogen will eventually die out.⁸¹ It is estimated that 80–86% of individuals in a population must be immune to polio for the remaining susceptible individuals to be protected by herd immunity. Herd immunity has obvious theoretical advantages for disease eradication but if routine immunization is stopped before eradication is achieved, the number of unvaccinated, susceptible individuals can rapidly exceed the capacity of herd immunity to protect them and new epidemics of disease can develop.

In 1988, the Assembly of the World Health Organization (WHO) – informed by the known science of the poliovirus, inspired by Rotary International’s 1985 pledge to completely eradicate polio, and undoubtedly influenced by their success in eradicating smallpox – established global eradication of polio by the year 2000 as a goal, giving birth to the Global Polio Eradication Initiative (GPEI). The Initiative is a public–private partnership of the World Health Organization, UNICEF, the Rotary Foundation, the US Centers for Disease Control and Prevention and the Bill & Melinda Gates Foundation.⁸²

The original GPEI plan was organized around three parallel strategies: to achieve high infant vaccination coverage with the oral polio vaccine (OPV); to conduct supplementary mass vaccination campaigns for children in polio-endemic countries and other countries with active wild polio virus (WPV) transmission, with “mop-up” vaccination campaigns in focal geographic areas around any confirmed polio cases; and to continue ongoing surveillance for acute flaccid paralysis and confirmation of polio diagnosis by testing stool samples plus environmental surveillance using sewage testing for polioviruses.

The GPEI made rapid early progress, with a reduction in the number of polio-endemic countries from 125 in 1988 to 10 in 2001, including polio-free certification in the Americas (1994), Western Pacific Region (2000), and Europe (2002). By 2001, 575 million children (almost one-tenth the world’s population) had received the oral polio vaccine.⁸² This required major public health education and immunization campaigns in countries all over the world and was not accomplished without adversity. Even with the express support of political leaders, polio workers had been kidnapped, beaten, and assassinated and still, pockets of disease persisted. The goal of eradication by 2000 was not achieved, and the Initiative struggled during the next decade due to recognition of disease caused by circulating vaccine-derived polio viruses and major programmatic challenges including the lack of basic health infrastructure limiting vaccine distribution and delivery; the crippling effects of civil war and internal strife; physically isolated population pockets; and the oppositional stance taken by some marginalized communities against what was perceived as a dangerous external intervention.⁸

Polio caused by vaccine-derived polio viruses is the most important of these problems. Recognition that new polio virus mutations could develop from the OPV and cause disease occurred early after the introduction of the OPV when cases of VAPP were first reported. This rare adverse outcome of oral polio vaccination occurs in what is now estimated to be one per million vaccinations, in either vaccinees or their close contacts. The risk of VAPP is highest after the first OPV dose and decreases sharply after that. Mutation and replication are time-limited in immunologically competent individuals with excretion of the OPV strains for only 30–60 days, so VAPP events occur in this early time frame.

Early in 2000, a different form of vaccine-derived poliovirus was recognized, arising from infection with OPV-derived virus strains with significant nucleotide sequence divergence from the original vaccine strains, reflecting increased virulence as a result of prolonged replication and transmission. Because the usual rate of spontaneous nucleotide substitution – genetic drift – in polioviruses is approximately 1% per year, poliovirus isolates that differ from the original strains in the OPV by more than 1% are defined as vaccine-derived polio viruses (VDPVs), and when these are detected in community contacts of vaccinees, they are called circulating VDPVs, or cVDPVs.⁸³ In immunocompromised individuals, these can cause prolonged infection in the original recipient but this has only rarely been associated with clinical disease – in this circumstance, these are called immunodeficiency-associated VDPVs (iVDPVs). In the more common cVDPVs, recombination is very

often observed as the mutated virus has been transmitted to multiple hosts with the opportunity to recombine with other human enteroviruses, especially coxsackie A viruses. Polio outbreaks caused by cVDPVs – recognized by the tragic appearance of cases of flaccid paralysis in a vaccinated region – are a critical public health threat and require the same emergent response as polio cases caused by wild polio viruses. Recognition of cVDPVs allowed identification of previous cVDPV outbreaks: retrospectively, cVDPV outbreaks were recognized to have occurred, including in Egypt between 1988 and 1993 and on the island of Hispaniola in 2000–2001. Since 2001, cVDPV outbreaks have been directly monitored by the WHO by stool testing cases of acute flaccid paralysis (AFP) and testing of environmental samples with approximately 90 identified cases/year; 86% of AFP cases due to cVDPV have been derived from strain 2 of the OPV.⁸³

Recent molecular genetic analysis of a data set of 424 vaccine-derived polioviruses from poliomyelitis outbreaks used genome sequence comparisons to evaluate how the attenuated type 2 strain in the vaccine evolves into a virulent strain capable of producing acute paralysis. With phylogenetic mapping, the researchers showed that within 14 days after vaccination, important gate-keeper mutations have already occurred, followed within months by multiple recombination events, presumably with other intestinal viruses. As with the influenza virus, these results show once again the importance of mutation by genetic shift in establishing virulence in RNA viruses. Findings in a tissue culture model suggest that a relatively small number of early transition mutations followed by recombination can rapidly transform the attenuated vaccine strain into a virulent pathogen.⁸⁴

With determined efforts at international, national and local levels, progress at eradication was sustained and by 2006, only four countries in the world (Nigeria, India, Pakistan, and Afghanistan) were reported to have endemic poliomyelitis cases due to WPV. A relatively small number of cases continued to occur in other countries, attributed to importation of the wild virus. Each year until 2010, approximately 1500–2000 cases of polio were reported, with 80% occurring in the four endemic countries. By 2012, India completed its first polio-free year and was declared polio-free. However, in the three remaining countries – Nigeria, Pakistan, and Afghanistan – endemic WPV transmission has never been interrupted. Despite all efforts, case counts increased, and importation of the poliovirus from these countries continued to cause outbreaks in countries that had been polio-free. In response, the World Health Assembly declared global polio eradication “a programmatic emergency for global public health” in 2012 and in late April of 2013, the WHO announced a \$5.5 billion, 6-year cooperative plan (called the 2013–18 Polio Eradication and Endgame Strategic Plan) to eradicate polio from its last reservoirs. The plan called for mass immunization campaigns in the remaining endemic countries. It also dictated a planned switch to inactivated virus injections, to eliminate the risk of cVDPV outbreaks.⁸⁵

The “declaration of polio eradication as a public health emergency” initiated new emergency operations in GPEI partner agencies, designed to complete eradication in the last three remaining polio-endemic countries. With these renewed

efforts, the South-East Asia Region was certified polio-free in 2014 and the proportion of the world population living in polio-free regions reached 80%. However, cases of acute flaccid paralysis caused by vaccine-derived polioviruses increased, sometimes exceeding cases due to the wild poliovirus. In response, the 66th World Health Assembly endorsed the *Polio Eradication and Endgame Strategic Plan, 2013–2018*, aimed at complete poliovirus eradication by elimination of all paralytic polio due to infection with either wild PV or cVDPVs.⁸⁶ In September 2015, the Global Commission for the Certification of Poliomyelitis Eradication (GCC) announced that wild poliovirus type 2 (WPV2) had been eradicated worldwide, after reviewing formal documentation submitted by Member States, global poliovirus laboratory network and surveillance systems. The last detected type 2 wild polio virus dated all the way back to 1999, from Aligarh, India.⁹

Global eradication of polio will require cessation of all oral polio vaccine. This process began in 2016 with removal of the type 2 strain by means of a switch from trivalent OPV (containing all three serotypes) to bivalent OPV (containing only types 1 and 3) in OPV-using countries. This was accomplished by a coordinated global switch beginning on April 8, 2016: amazingly, 155 countries that used the trivalent OPV switched to the bivalent vaccine by May 12, 2016. At the same time, the inactivated polio vaccine (IPV) was added in all routine immunization programs where the wild polio virus had been eradicated, to maintain immunity levels to type 2 polio (IPV is the original Salk trivalent vaccine manufactured from all three inactivated/killed vaccine strains.) A global stockpile of monovalent OPV type 2 (mOPV2) was maintained to enable a rapid response if vaccine-derived type 2 poliovirus emerged, following the switch. All wild type 2 polio virus and all Sabin type 2 viruses remaining in essential research facilities were secured under appropriate biocontainment levels to minimize the risk of accidental reintroduction.⁸⁶

Progress remained precarious. In 2016, four cases of acute paralysis due to wild polio virus type 1 occurred in Nigeria, where the terrorist organization Boko Haram has blocked vaccine efforts and surveillance. These were the first WPV cases in that country since 2014. Pakistan reported 20 WPV cases and Afghanistan 13 cases in 2016, compared with 54 in Pakistan and 20 in Afghanistan in 2015. Both countries are politically unstable and there are trust issues with vaccinators, associated with increasing numbers of inaccessible, susceptible children. One fifth of the paralytic polio cases in the world occur in one small district of Afghanistan where vaccinators have been unable to reach children consistently for the last 4 years.^{87,88} Efforts to eliminate all WPV continued.

But polio cannot be eradicated until vaccine-derived polio virus is also eliminated and cases of vaccine-derived disease continue to emerge in areas where population vaccination levels are low. Polio vaccine protects children from vaccine-derived strains of the virus just as it protects them from regular polio – but at the same time, use of the live, attenuated vaccine introduces new polioviruses which can mutate and cause polio outbreaks when there are sufficiently large numbers of unimmunized individuals to allow circulation of the vaccine-derived viruses. In 2015–2016, there were multiple cases of vaccine-derived poliomyelitis in the

Lao People's Democratic Republic (Lao PDR, formerly Laos) after no cases there for many years. After an intensified vaccination effort, the GPEI declared the Lao PDR officially free of circulating-vaccine derived polio virus. But in 2017, there were nine cases in the Democratic Republic of the Congo and tragically, in mid-2017, multiple cases of acute flaccid paralysis due to vaccine-derived polio virus type 2 were reported in war-torn Syria. It was 18 years since the last cases of polio in Syria, but immunization rates had plummeted during the civil war from over 80% in 2011 to just over 40% in 2017.⁸⁹ The WHO mounted a massive campaign aimed at vaccinating more than a quarter of a million children in eastern Syria beginning in the summer of 2017: the goal was to reach every child below 5 years of age with two doses of two different polio vaccines, spaced one to two weeks apart, a formidable challenge anywhere but especially in that chaotic, risk-filled situation. Despite the extreme risks associated with large-scale military movements, deficient health infrastructure and personnel insecurity in an active war zone, the World Health Organization, Gavi, UNICEF, and the GPEI reported that the polio outbreak in Syria had been completely interrupted by December 2018, without international spread.⁹⁰

Unfortunately, Syria was not the last of the new outbreaks. Since 2017, cases of AFP due to both WPV and cVDPV have increased. In 2018, WPV1 cases increased in both Afghanistan and Pakistan, a total of 33 cases in 2018 and 55 by August in 2019 compared with 22 in 2017, according to WHO reports. Disturbingly, environmental surveillance in this area documents clusters of persistent mutated genetic variant viruses in core reservoirs along the shared transnational border area between these two countries.

Cases due to cVDPV were documented in nine countries in 2018, a dramatic increase from all previous years. Indonesia and Papua New Guinea (PNG) reported a total of 27 AFP cases due to cVDPV1 after more than 10 polio-free years. Most disturbingly, seven African countries – Democratic Republic of the Congo, Kenya, Mozambique, Niger, Nigeria, Syria, and Somalia – have experienced polio outbreaks due to cVDPV2 between January 2017 and March 2019, indicating inadequate population immunization against the type 2 strain before the 2016 global switch from trivalent to bivalent OPV. When the type 2 strain was eliminated from the OPV, the GPEI anticipated that some cases of AFP due to cVDPV2 would appear and they thought they were prepared to address this situation with an mOPV2. However, the dramatic upsurge in type 2 outbreaks in Africa has almost depleted the stockpile of mOPV2 at a time when eliminating the type 2 strain from the OPV means an increasing number of children lack immunity to that strain. The inactivated Salk vaccine (IPV) is an obvious but suboptimal option because it is more difficult to deliver – requiring a series of three shots – and does not induce mucosal immunity. Emergent supplemental immunization programs were initiated in every instance but continued case identification indicates that these responses have either been too little or too late.⁹¹

In response, the WHO adopted the *Polio Endgame Strategy 2019–2023*, yet another updated plan – with yet another deadline – for global polio eradication

designed to address the dual challenge of wild polio virus eradication and elimination of circulating vaccine-derived polio viruses.⁹² Key features include a schedule for phasing out the oral polio vaccine and thereby ultimately eliminate vaccine-derived cases. The WHO and UNICEF will develop Rapid Response Teams capable of responding immediately with emergent vaccination campaigns if/when polio outbreaks occur. A partnership is being established in the Eastern Mediterranean region to support the National Polio Eradication Initiatives in Afghanistan and Pakistan. Problems with vaccine delivery in this area are formidable with the border area between Afghanistan and Pakistan functioning as one block with the population and the virus moving easily from one country to another. Limited health infrastructure, inaccessibility, political upheaval, and in Afghanistan, ongoing conflict, make vaccination progress exceptionally difficult. There is active resistance directed by local leaders and an ongoing disinformation campaign. Polio vaccinators in Pakistan must have police escorts and even with this protection, attacks against immunization teams are on the rise. Nonetheless, 1.07 million children were vaccinated in Pakistan during the 2019 May Case Response Campaign and 1.4 million children were vaccinated at 408 Permanent Transit Points along the border with Afghanistan. Aggressive political and diplomatic efforts to re-establish the immunization program in southern Afghanistan and to complete eradication in Pakistan are ongoing, but the Eradication Initiative is facing unprecedented obstacles in this area. After years of steady progress and more than 16 billion dollars, the GPEI is now facing its biggest challenge.

Before the GPEI began, poliomyelitis was endemic in 125 countries around the globe and more than 350,000 children per year were paralyzed for life. There has been dramatic progress towards polio eradication but the final steps are proving just how formidable an opponent the poliovirus can be.

Post-Polio Syndrome

Post-polio syndrome (PPS) is a serious constellation of symptoms that can occur in polio survivors many years after recovery from their initial episode of paralytic poliomyelitis. The syndrome was first described in the 1960s and criteria for diagnosis were established in 1972: (1) prior paralytic poliomyelitis with evidence of motor neuron loss; (2) a period of partial or complete functional recovery after the acute illness, followed by an interval of at least 15 years of stable neuromuscular function; (3) slowly progressive, persistent new muscle weakness or decreased endurance, with or without generalized fatigue, muscle atrophy, or muscle and joint pain; (4) symptoms lasting at least a year; and (5) exclusion of other neuromuscular, medical, and skeletal causes. Approximately half of all patients with paralytic polio go on to develop PPS, with an average time to symptoms from the original polio episode of 35 years. Risk factors for development of PPS include more severe acute poliomyelitis paralysis, older age at acute polio attack, and greater physical activity in the intervening years.⁹³

The etiology and pathogenesis of PPS are unknown but it has been hypothesized that the new muscle weakness of PPS is related to degeneration of individual nerve terminals in recovered motor units. These recovered units have been over-extended for many years, compensating for missing units lost at the time of the acute illness. Progressive inability to maintain the increased work demands leads to symptoms of reduced muscle strength and eventually, atrophy. This explanation corresponds with the gradual but progressive symptoms and recognition that previously affected muscles are much more likely to be involved. Generalized weakness and disproportionate fatigue are also common. New symptoms can also include respiratory insufficiency, difficulty swallowing or speaking and loss of vocal strength in individuals who had bulbar involvement at the time of their acute episode.⁹³

There are currently no effective pharmaceutical treatments that can stop the deterioration or reverse deficits. However, multiple studies have shown that non-fatiguing exercise with rest periods can significantly improve mild to moderate muscle weakness. Aquatic exercise programs designed to avoid muscle overuse improve flexibility, strength and cardiorespiratory function. Use of assistive devices can also improve specific muscle and joint symptoms. Most patients with respiratory insufficiency respond to non-invasive positive pressure ventilation and do not progress to permanent, full-time ventilation. Finally, aerobic conditioning has been shown to improve cardiac function without causing adverse effects.⁹⁴

Since the last cases of acute poliomyelitis in developed countries occurred before 1980, the number of new cases of PPS in the United States is steadily declining.⁹⁵ However, the story with global polio is one of ongoing outbreaks with more than 20 million people living with the sequelae of poliomyelitis.⁹⁶ The world will continue to be challenged by the medical and rehabilitation needs of individuals with the sequelae of polio including PPS for many years to come.

Looking Back :: Moving Forward

Early in the twentieth century, small outbreaks of infantile paralysis metamorphosed from contained pockets of disease in developed countries into large and progressively larger polio epidemics in NA and Europe. Many polio survivors were marked for life, living with the tragic residua of the disease in wheelchairs, leg braces and even primitive respirators. At its peak in the 1940s and 1950s, polio paralyzed or killed over half a million people – mostly young children – in the developed world every year.

In response, major research efforts identified the causative poliovirus, the epidemiology and (ultimately) the pathophysiology of the disease. Within half a century of the first major polio epidemic in the United States, American researchers developed two highly effective vaccines and the incidence of polio plummeted. In addition, major societal events dramatically affected the course of the disease. When polio survivor Franklin Delano Roosevelt became president of the United States, he mobilized the American public to support research to prevent and treat the disease. With his leadership, nationwide grassroots fund-raising campaigns emerged,

campaigns so successful that they completely funded all the research which led to development of the two vaccines and established the practice of public philanthropy for scientific research. FDR played another important role in the polio story. Desperate to restore his own physical health, he focused attention on physical rehabilitation, which emerged as an important medical subspecialty, initially working to restore function, improve strength and teach compensatory skills to newly paralyzed polio survivors. The emergence of rehabilitation therapy is a legacy of FDR and a legion of determined polio survivors. Finally, as disabled polio survivors struggled to re-enter society, they galvanized the rise of social and civil disability rights. In developed countries, the legacy of poliomyelitis remains in ongoing medical philanthropy, the practice of modern rehabilitation therapy and the disability rights movement. With these successes, two effective vaccines and dramatically decreased polio cases, the history of polio reads like a success story.

It was only after the development of the polio vaccines that the world belatedly realized that polio was a global disease. From lameness surveys designed to identify flaccid paralysis, the unrecognized global incidence of polio cases was estimated to have been at least 600,000 individuals annually. Inspired by the success of the smallpox eradication campaign, the WHO established the Global Polio Eradication Initiative (GPEI) dedicated to complete eradication of the poliovirus since 1988.

Using the oral polio vaccine (OPV), this largest public health program in history has made dramatic progress. More than 2.5 billion children have been vaccinated against polio, with a global decrease in the number of poliomyelitis cases by more than 99% and a reduction in the number of polio-endemic countries from 125 in 1988 to three – Nigeria, Pakistan, and Afghanistan – by 2012. Nigeria is on the verge of being declared wild poliovirus (WPV)-free. But despite sustained efforts in Pakistan and Afghanistan, there have been new WPV cases every year, with a tragic upsurge in 2019.

At the same time, cases of vaccine-associated paralytic poliomyelitis have been recognized since 2000 due to spontaneous mutation of the attenuated virus strains in the OPV with consequent recurrence of neurovirulence and transmissibility. Called circulating vaccine-derived polio viruses (cVDPVs), these mutants are fully capable of infecting and paralyzing children. As long as the live polio vaccine is used, it will inevitably release potentially potent polioviruses into the environment, making eradication impossible. Where population immunity is low, these vaccine-derived viruses can mutate and circulate, resulting in polio outbreaks which are clinically indistinguishable from those caused by the WPV. Endemic circulation of the type 2 poliovirus has been eliminated and it was removed from the oral polio vaccine in 2016. However, in 2018, there were outbreaks due to cVDPV2 in seven countries in Africa, all due to the type 2 strain.

Eradication of polio will require complete elimination of the oral polio vaccine, a serious challenge especially in light of the known limitations of the killed virus vaccine. In May 2019, the WHO adopted the *Polio Endgame Strategy 2019–2023*, designed to address the dual challenge of wild polio virus eradication and elimination of circulating vaccine-derived polio viruses.⁹² There is progress in

development of new vaccines: two novel live attenuated monovalent oral polio vaccines are in clinical trials and there is research into development of a new killed-virus vaccine based on the three strains in the OPV.^{97,98} The Endgame Strategy also includes changes in policy and approach to address ongoing challenges to vaccine delivery.

The poliovirus is a formidable and enduring enemy. The quintessential characteristic of RNA viruses – their capacity for rapid and continuous mutation – prevents continued use of the attenuated virus vaccine that was such a critical part of the early success of the polio eradication effort. Each use of the bivalent OPV or the monovalent OPV2 seeds potentially new cVDPV outbreaks; this is especially true for the mOPV2, because there have been dramatic population decreases in strain-specific immunity since the type 2 strain was removed from the OPV.

The Global Polio Eradication Initiative is at a critical crossroads, faced with the need to maintain high population immunity while transitioning away from the OPV in the context of increasing wild and vaccine-derived poliovirus outbreaks. Success will require a better vaccine with no risk of pathogenic virus introduction and induction of improved mucosal immunity. Clinical and environmental surveillance and emergent vaccine response to disease outbreaks must be sustained because the threat of new outbreaks – and of international spread – persists as long as WPVs and cVDPVs exist. For complete eradication, an approach must be developed for the small population of immunodeficient individuals who chronically excrete the poliovirus and serve as a perpetual source. Research and development can address these issues, at least theoretically. But on the ground, deficient health infrastructure, spreading disinformation campaigns, violence against vaccination teams, and inaccessible populations isolated by geography or conflict are formidable ongoing challenges to achieving the polio eradication endgame. With all the decades of scientific, medical and public health expertise brought to this challenge, the poliovirus remains an enduring and daunting adversary.

HISTORIC PERSPECTIVE: RACE AND CLASS IN THE TIME OF POLIO

The story of the development of the polio vaccine and its application to American schoolchildren, resulting in the virtual eradication of the virus in this country and then throughout North America, is accepted as perhaps the biggest public health success story of the twentieth century. In the parlance of public health, the microbe was isolated, the vector identified, an effective vaccine developed and administered, and people stopped dying: a win-win-win. The truth is, as you have been reading, far more complex. The first historical focus in this chapter will bring to light ways in which the efforts to control polio mirrored serious class and race-based prejudices dividing American culture. The second will concentrate on what happened to disabled polio patients after the vaccine

proved effective, a long story that reminds us how little room people with disabilities are still given in our society.

It took a very long time for public health officials to accurately identify the means of transmission for the polio virus, and in the interim, many opportunities arose for existing socioeconomic biases to be mapped on to polio prevention. The dependence on an old, trusted, and problematic model for combating the spread of infectious diseases was part of the problem. This model, which was created by John Chadwick in the United Kingdom and expanded in the United States by Lemuel Shattuck (1793–1859), said that the poor were the population most affected by epidemic diseases because of the poor sanitary conditions of their homes and neighborhoods. This was actually a smart observation and produced important changes in American cities, such as mandatory garbage removal, the development and improvement of urban sewage systems, and in some cases, the faster introduction of running water in poor areas. And while it did not occur immediately after Shattuck's recommendations were published in *Report of a General Plan for the Promotion of Public and Personal Health* (1850), local boards of health did increasingly take control over aspects of public hygiene such as the disposal of dead bodies, the management of contagious diseases in schools, the licensing and oversight of physicians, and public quarantine. Shattuck's report, written primarily about Boston but containing observations about other cities (London) and the cost of disease upon society, certainly became the bedrock upon which the US Public Health infrastructure would be founded. Beyond its institutional strength and ability to tie in with existing municipal systems, another asset was that big public health gains could be made without having to know the specific microorganism causing a disease or the way it was transmitted. By improving public hygiene, including ensuring safe public water sources, improving sewage removal, and controlling pests such as rats and flies, Lemuel Shattuck and his public health workers did dramatically reduce the rates of diseases such as cholera and typhus. But their motivation to do this work was not solely to improve the lives of the suffering poor. In fact, protecting the wealthy from infection by the poor, who they might encounter in their homes as staff, in lower-level positions in their offices, and even in the street, was a significant motivator for Shattuck. Eugenics, which was gaining ground as a way to prevent the sick placing undue burdens on American society, was also part of these public health efforts. The campaign against tuberculosis, which gained momentum in the late nineteenth century, reflected the ways in which Shattuck's approach could encourage dangerous socioeconomic prejudices within American society.

A "Discussion on the Advisability of the Registration of Tuberculosis" recorded in *The Transactions of The College of Physicians in Philadelphia* from 1894 reveals some of the ways in which race, class, and eugenics could

become intertwined in public health discussions.⁹⁹ This debate occurred between noted physicians of the time, and the subject was whether people with consumption (tuberculosis) should be reported to the Board of Health. It is noteworthy that the College agreed that they should not because it would be “adding hardship to the lives of these unfortunates, stamping them as the outcasts of society.”⁹⁹ This realization gives credit to the men involved in the debate, and it demonstrates an awareness of the long-term consequences quarantine or the label of “carrier” or “patient” could place upon people. Dr. Owen Wister terms the registration of patients “criminals guilty of consumption” who could face mob violence if the press encouraged an uproar over a growing number of cases.^{100,101} The tenor of the debate itself, however, is problematic. First, there is no agreement about how tuberculosis was transmitted. While Robert Koch had just discovered the tubercle bacillus, many still believed that it was genetically transmitted. Others believed that it was passed through sputum coughed up by sick patients, and some of those believed that the only way to prevent its passage was the careful management of sputum (both at home and, of course, in the streets) and the disinfecting of homes after a tuberculosis patient died. Noting the prevalence of tuberculosis cases in poor districts and even in specific residences, these physicians urged the board of health to take action only by “disinfection of rooms in which consumptives have lived and died.”^{99,102,103} The socio-economic biases emerge throughout the document, beginning with the assertion that the debate over registering consumptives need only apply to the poor, because the wealthy could be counted on to have responsible physicians manage the disinfecting of their homes after their death. The eugenics aspect emerges in response to the claim that tuberculosis was hereditary. Dr. Da Costa, for example, insisted that no public health measure other than the absolute refusal to allow tuberculosis patients to marry would prove effective. Black people, who lived in the poorest area of the cities under investigation and were thus doubly in jeopardy of having tuberculosis, were described as even less capable of basic hygiene than the white poor, a group defined as lacking even the most basic capacity for personal or interpersonal care because of limited means and abilities (“the poor and careless”). To borrow Dr. Wister’s phrase, labeling a group as infected with a contagious disease made them into criminals. And even in the discourse of these learned physicians, the poor and the non-white are suspect before they show the first symptom. It comes as little surprise, then, that during the polio epidemic, these very individuals were once again suspected of endangering public health.

As Naomi Rogers ably demonstrates, the 1916 New York City polio epidemic reflected the racist and anti-immigrant anxieties reflected in the tuberculosis debates. Despite strong epidemiological evidence that polio disproportionately affected American-born white children living in areas

with good sanitation, public health efforts in New York focused on poor, immigrant neighborhoods, especially Italians, whose neighborhoods were plagued by filth.⁹⁹ Nancy Tomes also identifies the role of this kind of thinking in public health efforts to control polio. Flies became a focus of polio eradication efforts from the epidemics during World War I well into the 1940s, with officials believing the insects originated in filthy, poor neighborhoods and carried the disease to the upper-middle-class neighborhoods, where it thrived. Underneath this fear of insects also lay anxiety about black and immigrant servants who worked in the predominantly white, wealthier suburban homes where polio struck hard.¹⁰¹ The tendency to close public swimming pools and playgrounds, where children of different classes and races could mix, served two masters. First, the obvious epidemiological approach to controlling contagious diseases with poorly understood modes of transmission is to limit contact among vulnerable people. By closing public places such as swimming pools and movie theaters, where children from different backgrounds might mingle, the hope was that poor, immigrant children from areas with poor sanitation could not infect wealthier, native-born children. More traditional quarantine methods, in which houses with active polio cases were required to identify themselves with window placards, were also used throughout the earlier twentieth century and, although they would certainly have resulted in the isolation of members of those households, they were less racially and socioeconomically divisive, because the majority of affected homes were in white, wealthier suburbs.

Naomi Rogers once again provides an important corrective to our understanding of the racially motivated public health efforts directed toward polio.¹⁰² While it was predominantly understood to be a white disease through the 1930s, this reflected prevailing racial bias that claimed black people could not contract polio and came at a very high price for African American victims of the disease. A combination of factors made African American polio patients disappear from the polio narrative that dominated the first three decades of the twentieth century. First, the South, where the majority of African Americans lived, did have a lower incidence of polio outbreaks than the Midwest and the Northeast. But that does not explain why black people were excluded from public health and patient records in areas that were affected by epidemics. One of the reasons was the continued predominance of racial medicine, which contended that people of different races had different susceptibilities to different diseases, and that African Americans could not contract polio. Second, African American communities were primarily served by black physicians, and white medical schools did not admit them. Thus, they lacked access to the same level of education as those physicians serving white neighborhoods. African Americans were also socioeconomically disadvantaged, and thus less able to seek treatment

until the disease advanced. Morbidity and mortality statistics were not as aggressively reported from these communities, and polio cases easily dropped through the cracks.

Finally, most of the treatment centers for polio patients, including the one in White Springs, Georgia that was founded by President Roosevelt, only accepted white patients. Beginning in the 1930s, civil rights activists and African American physicians began to counter the narrative that polio did not affect African Americans, and although the predominant treatment centers continued to rely on the “susceptibility narrative” of racial medicine, the increasing visibility of African American polio victims became hard to ignore, especially as FDR faced his third presidential election and hoped for an unprecedented level of black support. This oversight was partially remedied finally in 1939 when the Tuskegee Institute received a grant from the March of Dimes to open a center for treating black children with polio. It opened in 1941, promising to train African American physicians to treat polio and other orthopedic diseases as well as treat all affected children. In fact, with only 36 beds and minimal outpatient facilities, the center was insufficient to treat even a fraction of non-white polio patients. The Center did, however, become an important part of national efforts to correct the racialized approach to polio. John Chenault, the African American orthopedic surgeon chosen to head the center, countered the prevailing epidemiological studies that demonstrated how rare the disease was in African American communities. In his own study focusing on epidemics in the South, he showed that African American cases had been significantly under-reported due to medical oversight and lack of resources.¹⁰³ The 1940s was a decade of conflicting racial accounts about polio, with the old “racial susceptibility” argument still holding sway in a great deal of popular reporting on the disease and in the medical community. Separate medical facilities for people of different races remained the hallmark of American medicine through the 1960s, especially in the South, but increasingly the efforts to eradicate polio attempted to bridge this divide. The March of Dimes responded to Chenault’s efforts and the increasing visibility of black polio victims resulting from civil rights efforts by attempting to integrate black children into its polio advertising and fundraising efforts. Rita Reed became the first African American poster child for the March of Dimes in 1947. Amazingly, by the time Salk’s vaccine was introduced in public schools, black and white children received it equally and black medical professionals were an integral part of the trials. In the South, however, 1954 was the year *Brown v Board of Education* ended school segregation, and black children received their vaccines on the lawns outside white schools because they were not yet permitted inside them.

Historic Perspective: Physical Disability Before Polio

The story of the polio vaccine is one of scientific triumph. Without question, the administration of Salk's vaccine to children through the public school system eradicated the virus in the United States and Canada. What it could not do, however, is bring back full mobility to those who had already been affected by the virus. Polio survivors were caught in an impossible landscape, in which the physical marks of their illness often defined their existence. Before polio, children born with physical disabilities or degenerative diseases such as cerebral palsy were frequently sent to institutions or kept at home. Public schools were not required to accommodate wheelchairs or any other forms of mobility assistance, and thus a standard education often fell beyond the reach of polio victims. For those who spent their childhoods in institutions, access to academic curricula was often limited or non-existent. Patients with disabilities were not expected to require educations because they were not expected to work, marry, or have families of their own. Physical disability, as defined before the mid-twentieth century, was a life sentence to a very limited life indeed. Some of this reflects the eugenics theory discussed in the previous section. The general treatment of people with physical disabilities before the 1940s–1950s reflected eugenic thinking, which contended that anyone born with a disease or disability should be prevented from reproducing – either through isolation or sometimes forced sterilization – to protect the nation from having to support their “defective” offspring. The 1927 Supreme Court decision in *Buck v Bell* to uphold a 1924 Virginia law permitting the sterilization of those found to be “feeble-minded” or epileptic demonstrates the strength of eugenic thinking in the first half of the twentieth century.¹⁰⁴ Virginia was far from the first state to pass an involuntary sterilization law. That honor goes to Indiana, which did so in 1907, and 30 more states followed suit. The states that did not pass involuntary sterilization laws frequently proposed and debated them, demonstrating the prevalence of eugenic thinking in this country. In fact, Oliver Wendell Holmes' pronouncement that “three generations of imbeciles are enough” allowing the forced sterilization of anyone deemed to fit the very loose category of “feeble-minded” still stands, although the state laws it upheld were finally repealed, with some still in place as late as the 1970s. Throughout its use, involuntary sterilization affected at least 70,000 people in this country, with reported numbers thought to be low because of the prevalence of sterilization within institutions that operated outside the law. Women were disproportionately the victims of forced sterilization, as were racial minorities and the poor. While those deemed to be mentally ill were the most common victims of this, the “feeble-minded” were a close second.¹⁰⁵ Forced sterilization of people with physical

disabilities was rare, but their institutionalization was encouraged and accepted by the time the polio epidemic reached its height in the United States in 1952.

Polio changed the way America understood physical disability because the campaign to end it was so extensive, thanks to the March of Dimes, and because the virus was so prevalent that nearly everyone knew someone affected by it. Those affected in the final rounds of epidemics that occurred before Salk's vaccine came into effect had the numbers and visibility to produce a shift in American thinking about physical disability, much as the images of children in braces produced a shift in American charitable giving to end the disease. But it was not an easy transition to bring about, as Daniel Wilson demonstrates. Three primary challenges faced the families of polio survivors and the patients themselves as they returned home from rehabilitation facilities and tried to re-enter their lives. First, they were among the first people with physical disabilities other than war veterans to have lives to return to from the time before their disabilities. Men stricken with polio wanted to return to their jobs, if those were still available, or find some other means of making a living so they could help support their families and preserve their identities. Women afflicted by the virus hoped to marry and become parents or, if they were already wives and mothers, return to those roles. Adolescents and children, both male and female, wished to return to school and play with their friends. But decades still existed before the Americans with Disabilities Act (1990) would make accessibility a requirement for public facilities, and there were no legal requirements prohibiting hiring discrimination for those with disabilities. Schools and office buildings were a labyrinth of staircases, heavy doors, and narrow doorways that made wheelchairs incredibly difficult and crutches a daily challenge. Physical education requirements, the centrality of athletics in school social activities, and negotiating dating as polio patients entered high school was an additional challenge.¹⁰⁶ The will and family support required to reintegrate those left disabled by this virus into the worlds they left behind were as exceptional as they were novel. Previous generations of polio survivors, like those born with physical disabilities or who suffered injuries at work or in the military, had largely lived quiet lives at home or, in extreme cases, in institutions. Polio survivors paved a new road for the physically disabled, living and working in "normal society."

The second challenge they faced in entering public life was acceptance. Not everyone agreed that people afflicted with the marks of the virus should be working or going to school, although the March of Dimes campaigns consistently featured children in braces or on crutches enjoying childhood activities. Larry McKenzie, for example, was the 1951 March of Dimes poster boy, and he was featured studying at the kitchen table on his family's farm and sharing a toasted marshmallow with a friend,

all while wearing elaborate braces to support his arms.¹⁰⁷ Some families found themselves and their disabled children ostracized long after the possible threat of contagion had passed, as though the bad luck that had affected the family was itself contagious. Everyone affected by the disease faced the social stigma surrounding “cripples,” the term applied to anyone with a physical disability. As Wilson puts it, “Because negative attitudes about individuals with disabilities were widespread in society, every encounter outside one’s intimate circle risked rejection.”¹⁰⁸ That rejection included stares, chastisement for being out in public at all, and even public declarations thanking god for protecting the viewer from winding up affected as the survivor had been.¹⁰⁸ Those who could hide their braces under shirtsleeves or pant legs were happy to do so, but those in wheelchairs or requiring respirators were stuck being immediately visible as a “polio,” the term applied to physically disabled survivors.¹⁰⁹ The most horrible cases of discrimination occurred in schools based in communities that reinforced existing stereotypes about handicapped people. While many schools allowed polio survivors back into their classes as soon as they were able to return, although they did nothing to help them negotiate the physical obstacles posed by the buildings themselves, others did not. Some segregated students with disabilities of any kind from regular classes, placing those with physical, cognitive, and mental disabilities in the same room with a single teacher. Others required students with disabilities to receive tutoring at home, either through teachers sent by the district (often resulting in a very haphazard education) or through speakerphone. Some districts simply refused to allow polio survivors to come back. The parents of a polio survivor in rural southern Wisconsin were told by their daughter’s school superintendent that it was not convenient to rearrange classes to accommodate her, especially as it was a waste of time to educate crippled children and it would be depressing for other children to see her. After two years of activism by members of her community and agreeing that she would not ask for any accommodations of any kind, she was allowed to return to high school. She was greeted by her homeroom teacher apologizing to the other students for having to see her every day. She persevered, navigating her wheelchair through a building that could not accommodate it and graduating without ever having been inside one of the bathrooms, as the doorways were too narrow for her to enter.¹¹⁰

The fact that polio survivors were expected to fit into their surroundings, work hard, and hide their disabilities was a mixed blessing. Certainly, these individuals went on to live remarkable lives, often earning top grades in school and embarking upon university education and respected professions. But the cost of fitting in was very high. It took several decades of trying to be accepted as “normal” before survivors began to look for other people like them or even identify themselves

as handicapped, because their fear of rejection was understandably very high. By choosing to fit in as much as possible, they also overstressed their bodies. The extremely hard work they put in during their rehabilitation to walk, use their legs and arms without visible braces, and even to breathe on their own would later show up as post-polio syndrome, when their overworked neural pathways began to degenerate.

The final challenge they faced was one they shared with other disabled individuals: making the world accept them on their own terms. It is not surprising that this took a very long time. While it is true that the majority of polio survivors were part of the Baby Boom generation that is renowned for breaking away from the conservative ethos of previous generations, forming a movement to gain disability rights required something other than bravery and a belief in the fundamental importance of justice. It meant publicly acknowledging that you were physically different and thus deserved accommodation to allow you to live your life to the fullest possible potential. It meant coming out of the shadows, wearing braces or using wheelchairs in public, and talking about what polio cost you. In short, it meant rejecting the Puritan work ethic instilled in so many survivors during rehabilitation, where they were told their ultimate goal was to seem normal, and that they could only accomplish it by working as hard as possible. Any failure to achieve physical therapy goals was interpreted as a failure of the patient's will, and thus patients were held responsible for their own recovery. The positive side of this is that it inspired patients to believe they could get better, sometimes in the face of extraordinary odds. But the negative side was omnipresent: few polio survivors regained complete use of their bodies, and they were blamed for that. Choosing to publicly claim the identity of a disabled person meant rejecting this dictum, which so many had adopted as children or teenagers and not been able to question. It also meant accepting your body as it was – not as it had been born, as was the case for other civil rights movements and even many people with congenital disabilities, but as it had been transformed by a virus. The plethora of polio survivor narratives now available through the internet demonstrates the challenges these people encountered as they struggled to return to their lives, find meaningful work, marry, and have families. The narratives show the extraordinary strength of these individuals and, at the same time, makes you see them as people whose bodies were hijacked by a virus but whose hearts, minds, and souls remained inextricably their own.^{111–113}

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6

HIV AND AIDS

The Never-Ending Story

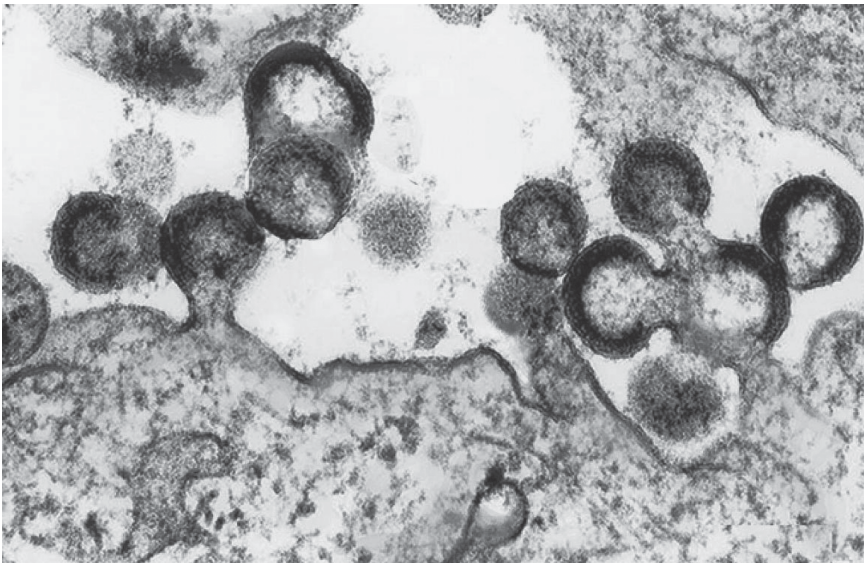


FIGURE 6.1 HIV virions budding and releasing from an infected cell.

Source: NIAID, NIH

BLOOD IN THE OR

I have always loved the operating room. I'm a pediatric cardiologist, not a surgeon, but most of my critically ill patients were babies with heart defects for whom surgery was the only effective treatment. Congenital heart defects occur because of the complex process of cardiac development that begins in the early weeks of pregnancy. The heart develops from a tiny tube that folds and twists and involutes and expands to ultimately reveal the four chambers of the normal heart that receive blue blood back from the great veins and pump oxygenated red blood from the lungs out to the body. An error in cardiac development at any stage can result in a defect in the heart's structure – and in some newborns, these defects are fatal without emergent correction. When I started in pediatric cardiology, congenital heart surgery was just out of its infancy and pediatric cardiovascular surgeons were beginning to attempt complete repairs in newborn infants with critical structural defects when no other good option was available. In those days, the field was still new and very small so cardiologists and cardiovascular surgeons worked together very closely. Cardiologists made the baby's diagnosis using cardiac catheterization, a technique that involves threading a tiny catheter from the blood vessels in the leg up into the heart where radio-opaque dye is injected to visualize the anatomy in detail. Once the diagnosis was established, cardiologists met with the surgeon to plan the surgical approach. My teachers – pioneers in the field of pediatric cardiology – always went to the operating room with their patients and so did I. After all, besides the surgeon himself, the cardiologist was almost always the only other person in the operating room who understood the problem.

I am talking here about open heart surgery – and when the heart is the size of a golf ball as it is in a newborn baby, this means some of the most technically challenging procedures imaginable. Open heart surgery is exactly that – opening the heart to perform surgery – and this means that the heart has to stop beating and the body's circulation has to be supported for the surgeon to work. This is accomplished with a heart–lung or cardiac bypass machine to which the unoxygenated venous blood is directed as it drains above and below the heart. The bypass machine oxygenates the blood, simulating the way the lungs function in life, and then routes it through a tiny catheter – smaller than a drinking straw in a newborn – into the aorta, the great vessel that carries blood away from the heart. A roller pump drives the oxygenated blood from the heart–lung machine through the aorta, to the heart muscle itself and to the entire body. It is cardiac bypass that allows the surgeon to stop the heart, visualize the anatomy and correct the defects.

The heart revealed is a thing of great beauty, lying just under the breastbone, pumping continuously from the first weeks of pregnancy to the end of life. It has always been a magical moment for me to see the anatomy that

I had worked to diagnose revealed, and to watch the intricate steps involved in cardiac repair. My respect for the courage and skill of pediatric cardiovascular surgeons still verges on reverence. When the repair has been completed and the heart begins to pump again, I am always filled with awe. After all these years, open heart surgery in a newborn still feels like a miracle.

But open heart surgery does expose the operating team to an enormous amount of blood. Every step involves blood – venous blood flowing, arterial blood pumping, random blood splashing – and sharp objects: saws, needles, scalpels, retractors. There is obvious, ongoing risk of trauma to the hands, evading protective gloves, of blood spurting onto the face, into the eyes. Many times, I remember seeing a surgeon's forehead dotted with blood above his mask. Blood exposure was always an issue, but it suddenly became a major risk after the AIDS epidemic began. Our knowledge about AIDS in medical practice followed the epidemiologic pattern as it was uncovered by reports in the literature. At first, it was a strange new disease that attacked the immune system of young gay men causing unusual infections and malignancies – a problem for specialists in infectious disease and oncology. But less than a year after the very first cases, AIDS was reported to be caused by a transmissible agent carried in the blood – and suddenly it became a problem for all healthcare providers and especially for surgeons. Because the agent had not been identified there was no way to test for its presence and AIDS cases occurring after blood transfusions showed the agent was present in the blood supply. Open heart operations using cardiopulmonary bypass represent the largest routine exposure to blood in clinical medicine, so cardiac surgical teams were thought to be at the greatest risk of accidental infection with the unknown agent that caused AIDS. Cardiac surgeons are among the bravest people I know, routinely facing the challenge of literally stopping the heart to repair it – but I have never seen fear like that I saw in the faces of my colleagues during those terrible early years of the AIDS epidemic. For adult cardiac surgeons, the possibility of exposure was even greater because intravenous drug users were at high risk for both AIDS and infected heart valves requiring urgent open heart repair. Early in the epidemic, an anonymous survey of cardiac surgeons suggested that almost 30% would not operate on a person with AIDS because of fear of infection.^a

The dilemma of the contaminated blood supply continued from 1982 until 1985, long after the human immunodeficiency virus had been identified because of the conflicting priorities of the key groups involved: the public health community led by the CDC were convinced of an impending disaster involving potentially many thousands of recipients infected by contaminated transfusions of blood and blood products while the blood-banking community was concerned about fear of AIDS compromising their critical supply of donors. Without a definitive test, potential solutions were suggested and rejected while doctors struggled to deal with terrified patients and families

as well as their own fears. During this time, many adults donated their own blood in advance of an operation, a complicated effort that involved going to a blood bank weeks before surgery when up to three units of blood could be taken and stored. Obviously, this was not an option for children or in an emergency situation so the process of directed donations arose in response to concerns about blood safety raised by the AIDS epidemic. A directed donation occurred when a patient's family and friends donated blood to be used only for that specific patient. Directed donations were extremely common before open heart surgery in the children I cared for in the early 1980s.

By 1985, an effective HIV screening test had been developed and within 6 months, the blood supply was declared safe – but not until more than 12,000 people in the United States had received contaminated transfusions of blood or blood products. By that time, the healthcare industry had a much greater understanding of the risk of infection related to multiple procedures including simple routine tasks like blood drawing. In terms of surgery, the procedures that exposed surgeons and their assistants to infection from contaminated blood had been found to primarily involve passing devices between operators, with the highest risk associated with suture needles followed by scalpel blades and glass syringes. In a study of 234 observed surgeries, an astonishing 50% were reported to involve glove perforation with contamination of a co-worker's hand with blood.^b A 1992 glove study showed 51% hand contamination with single gloves versus 7% with double gloves – this report led to implementation of double gloving as a routine universal precaution along with masks with shields that protect the eyes.^c Between 1985 and 2013, the CDC reported there were 58 confirmed and 150 possible cases of occupationally acquired HIV infection among American healthcare workers. Nurses were the largest affected group, with 41% of confirmed cases; there were no confirmed cases in surgeons.^d

Pediatric cardiology progressed enormously during my time in the field – we almost always make the diagnosis of even the most complex congenital heart defects with ultrasound now, and surgical procedures that were revolutionary in the early days have become almost routine. Often, non-surgical, catheter-based procedures have replaced or augmented surgical approaches. And infection of the blood supply with HIV has been replaced by the risk of exposure to other serious viral pathogens like the hepatitis C virus.^e The risk for healthcare workers of HIV infection due to exposure to contaminated blood has all but disappeared, but this history remains an important part of the story of AIDS.

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HIV and AIDS: The Never-Ending Story

At first, it seemed like an American disease. In June 1981, the Centers for Disease Control and Prevention (CDC) in Atlanta reported in their *Morbidity and Mortality Weekly Report* (*MMWR*) that between October 1980 and May 1981, five young men in Los Angeles, all active homosexuals, were treated for biopsy-confirmed *Pneumocystis carinii* pneumonia (PCP). Three of these patients had evidence of depressed immune function and two died. *MMWR* is a weekly summary for the United States of important, time-sensitive public health information. In the comments accompanying this small case series, the editors noted that historically, *Pneumocystis* – a yeast-like fungus – infects only patients with severely compromised immune systems, so its occurrence in these previously healthy individuals raised the possibility of immune dysfunction secondary to some predisposing common exposure. That all of the patients were homosexuals suggested an association with some aspect of homosexual lifestyle or a disease acquired through homosexual contact.¹

From this first report, the CDC became the coordinator for emerging information on this new disease and *MMWR* the major information source as the knowledge base grew and evolved. Only 4 weeks after that first release, *MMWR* reported that over the last two and a half years, Kaposi's sarcoma (KS) had been diagnosed in 26 young homosexual men, 20 in New York City and six in California. Until that time, KS was known as a rare skin cancer that presented as circumscribed dark purple lesions and that only occurred in elderly men of Mediterranean descent – characteristics not shared by any of these young men. Notably, six of these KS patients had also developed *Pneumocystis* pneumonia. In contrast to the usual KS course where mean survival time was 8–13 years, eight patients died within 2 years of diagnosis.² By September, there was a second series of eight patients with atypical KS. Again, all were young homosexual men and survival time was short: half of the patients were dead within 20 months of diagnosis. The authors reported the historic association of KS with an immune-compromised state in a subset of cases in Africa, but no immune testing was performed in either of these two groups.³

The epidemiology of this new disease unrolled rapidly with critical new reports almost every month. By the end of 1981 – only six months after the first report – outbreaks of bizarre opportunistic infections and of unusual malignancies in young homosexuals had been reported from major cities all over the United States. By this time, these disparate cases were found to be linked by definite evidence of immune dysfunction focused on the cellular immune response of lymphocytes, the white blood cells that determine the body's response to infectious microorganisms and other foreign substances. The characteristic pattern was moderate to severe lymphopenia (low lymphocyte counts); specifically, low counts of helper/inducer T4+ lymphocytes – now called CD4 cells – and correspondingly, a low T4+ to T8+ lymphocyte ratio (T8+ lymphocytes are suppressor/cytotoxic lymphocytes, now called CD8 cells); and anergy (no lymphocyte response to antigen stimulation).

Then in December 1981, opportunistic infections associated with cellular immune dysfunction were reported for the first time in *heterosexual* men and women who were intravenous drug users (IDUs).⁴ The combined evidence indicated a new disease caused by a transmissible agent that attacked the immune system in specific, vulnerable populations. Most concerning was the exponential increase in cases and the expanding base of susceptible populations – by the end of 1981 in the United States, there were 270 reported cases of this severe, new, acquired immune deficiency among gay men and 121 of these individuals had already died.⁵

*Media coverage played a critical role in the evolution of the AIDS story. In the beginning, coverage of the new disease outbreak was very limited. Reports described a “new and mysterious illness” in gay men with little additional information. Quantitative content analysis of press coverage of HIV/AIDS in Australia, US, France, and Britain during the 1980s and 1990s revealed a common pattern with coverage focused almost exclusively on homosexuals.*⁶

*It is not a coincidence that AIDS emerged in the early 1980s when after centuries of persecution, the gay liberation movement was in full swing in the United States. For a minority of young homosexual men, liberation meant an extravagantly active sex life with multiple sexual partners in places like public bathhouses. In spite of gay pride parades and stories of “coming out,” the longstanding stigma of homosexuality persisted with overt homophobia through the 1980s, even in New York City and San Francisco, both sophisticated metropolitan centers with flourishing gay subcultures – and both among the first cities to report cases of the new illness. From the beginning, news coverage of the disease was dominated by the initial CDC reports of “gay pneumonia,” alluded to in 83% of stories in 1981.⁶ The labels “gay plague” and Gay-Related Immune Disease (GRID) first appeared in 1981, establishing the public view of the illness as exclusively a contagious disease of homosexuals.*⁷

On July 3, 1981, the same day this information was published in MMWR, the New York Times reported “Rare Cancer Seen in 41 Homosexuals,” describing the outbreak of Kaposi's sarcoma, “a rare and often rapidly fatal form of cancer,” diagnosed in homosexual men. The article – one of the first in a lay publication to address the new outbreak – explained that the diagnoses had been made mostly in New York City and San Francisco, and that the CDC was alerting other doctors who treat “large numbers of homosexual men” of the

problem.⁸ Beginning with the headline, the article clearly suggested that this cancer was a homosexual problem, just like the unusual infections and the immune system dysfunction.

Early in 1982, a small case series described immunologic findings in 15 healthy homosexual men and two men with KS. Both KS patients and seven of the 15 healthy gay volunteers had low T4+/T8+ (helper/suppressor) lymphocyte ratios – the same pattern seen in individuals with opportunistic infections and KS. High cytomegalovirus (CMV) antibody titers – evidence of previous CMV infection – were found in 14 of the 15 men and half of the group reported exposure to inhaled nitrites. A history of CMV infection and of amyl nitrite use had been noted in prior reports of both opportunistic infections and KS, and the authors of this report suggested the combination might be the cause of the immune dysfunction. It would be many months before this immunologic pattern was instead recognized as a pre-clinical stage of the new infectious disease.⁹

Within months, a series of critical reports raised new concerns about spread of the epidemic. First, the CDC reported that between June 1981 and May 1982, a total of 355 cases of KS and/or serious opportunistic infection had occurred in previously healthy people between 15 and 60 years of age. Sixteen per cent of the group were heterosexual and of these, the majority had a history of IV drug use. Similarities between the homosexual and heterosexual cases in age range, fatality rates, and geographic and temporal distribution strongly suggested that the cases were all part of the same disease outbreak.¹⁰

A critical report from the CDC in May 1982 described cases of persistent, generalized lymphadenopathy (lymph node enlargement) in homosexual males, reported by physicians from several major cities. In a subset of these men seen at medical centers in Atlanta, New York City, and San Francisco, immunologic evaluation demonstrated immune dysfunction with abnormal T-lymphocyte helper-to-suppressor ratios, the same pattern described in individuals with overt opportunistic infections and KS. Approximately 70% of these patients also had some constitutional symptoms including fatigue, fever, night sweats, and weight loss. One patient in the group went on to develop KS before the study ended. A direct relationship between the immunologic findings for these patients with lymphadenopathy and patients with opportunistic infections and/or KS could not be demonstrated, but the possibility was raised that this lymphadenopathy was an early expression of infection with the same transmissible agent attacking homosexual men and IV drug users.¹¹

Only a month later, the CDC reported the now familiar disease pattern of opportunistic infections (OIs) in 34 Haitians (33 males) living in the United States; most had immigrated within the last 2 years. Almost half the group had experienced multiple opportunistic infections. Age range was similar to other reported groups, but only a small minority were homosexuals or IV drug users. When immunologic studies were performed, there was severe T-cell dysfunction with a marked decrease of the T-helper cell subset and inversion of the normal ratio of T-helper to T-suppressor cells. For the entire group, the mortality rate on follow-up was nearly

50%. The similarity of the disease pattern and immunologic picture in Haitians recently entering the United States to that described in American homosexual males and IV drug users suggested an as-yet unidentified common cause.¹²

And a week after that, the CDC reported three cases of opportunistic PCP in individuals with hemophilia but with no other underlying disease. All three were heterosexual males who had received repeated injections of factor VIII concentrate to stop uncontrolled bleeding. To treat clotting factor deficiencies like those found in hemophiliacs, pooled concentrates of the missing factor from hundreds of donors are needed. None of these three patients had a history of homosexual contact or intravenous drug abuse, but two patients who were specifically tested had evidence of cellular immune deficiency and all had lymphopenia. The CDC editors of the report wrote,

The clinical and immunologic features of these three patients are strikingly similar to those recently observed among ... homosexual males, heterosexuals who abuse IV drugs, and Haitians who recently entered the United States. Although the cause of the severe immune dysfunction is unknown, the occurrence among the three hemophiliac cases suggests the *possible transmission of an agent through blood products*.¹³

By December 1982, the CDC reported that all three of the original hemophilia patients had died, and there were four more cases and one suspected case among hemophiliacs receiving frequent clotting factor transfusions; two were children under 10 years of age. All had the now familiar pattern of cellular immune dysfunction – profoundly depressed lymphocyte counts and reversed CD4:CD8 ratios. As noted in cases from all the other risk groups, antibodies to another viral infection – in this case, hepatitis B – were prevalent in the hemophilia patients.¹⁴ A national survey of hemophilia treatment centers revealed that 30% of all hemophiliacs had abnormal immunologic tests.¹⁵

With these cases, the evidence seemed clear that a dangerous new transmissible agent was attacking the immune system of healthy individuals in multiple different settings. At an urgent meeting convened in July 1982 to specifically address this risk in individuals with hemophilia, the CDC adopted the term “acquired immune deficiency syndrome” to describe the clinical and immunologic pattern in all these groups and the acronym AIDS was born.¹⁵

Another intriguing piece of the puzzle emerged in September with evaluation of immune function in 81 male homosexual volunteer research subjects in NYC: 50 were asymptomatic and 31 had one or more of the constellation of symptoms described in association with generalized lymphadenopathy. T-cell subsets were abnormal in both groups compared with those of a control group of healthy heterosexual males: T4/T8 ratio averaged 1.8 in the controls compared with 1.1 in the asymptomatic homosexuals and 0.8 in the symptomatic group. The T4/T8 ratio decreased as the number of sexual partners increased. Although not explicitly stated by the researchers, these results suggested that a large proportion of sexually active

homosexual males in NYC could already have been infected by the AIDS agent with significant but, to this time, asymptomatic immune dysfunction.¹⁶ The findings were a chilling premonition of what was to come.

In the September 24 edition of *MMWR*, the CDC provided the following case definition of AIDS which included recognition of a pre-symptomatic state:

AIDS is an opportunistic infection at least moderately predictive of a defect in cell-mediated immunity, occurring in a person with no known cause for diminished resistance to that disease. Such diseases include Kaposi's Sarcoma, *Pneumocystis carinii* pneumonia, and other serious opportunistic infections. ... this case definition may not include the full spectrum of AIDS manifestations, which may range from absence of symptoms despite laboratory evidence of immune deficiency to non-specific symptoms (e.g., fever, weight loss, generalized, persistent lymphadenopathy) to specific diseases that are insufficiently predictive of cellular immunodeficiency to be included in incidence monitoring (e.g., tuberculosis, oral candidiasis, herpes zoster) to malignant neoplasms that cause, as well as result from, immunodeficiency. Absence of a reliable ... test for AIDS makes th(is) working case definition the best currently available for incidence monitoring.¹⁷

By December 1982, the potential number of "at-risk" groups had increased even further, with the report of AIDS in a 20-month-old baby who had unexplained cellular immunodeficiency and repeated opportunistic infections after multiple blood and platelet transfusions for Rh incompatibility as a newborn. One of the platelet transfusions the baby received was ultimately found to have come from a homosexual man who was well when he donated blood but who died of AIDS-related opportunistic infection 17 months later.^{18,19} This case was a bombshell suggesting not only transmission of the infectious AIDS agent in blood transfusions but also a long incubation period for the infectious agent before symptoms appear.

Only a week later, a whole new risk group emerged when the CDC reported four cases of AIDS in babies less than 2 years of age. None had ever received blood or blood products, but three had mothers from groups at risk for AIDS and the mother of the last child had AIDS. In addition, the cases of six young children who died with opportunistic infections and unusual cellular immunodeficiencies were also under investigation, as were those of another 12 children with similar immunodeficiencies but without life-threatening opportunistic infections.²⁰ Clinical features in these infants included growth failure, oral candidiasis (fungal infection), enlarged liver and spleen, generalized lymphadenopathy and chronic pneumonitis without a demonstrable infection. Seven of the nine mothers for whom information was available were intravenous drug users.

The pattern of immune dysfunction described in these infant AIDS cases closely resembled that seen in adults with AIDS. One mother had already died with AIDS and the others came from groups at risk for AIDS. Taken together, these cases suggested the infectious agent had been transmitted from mothers with AIDS or a

pre-AIDS high-risk state to their children before birth or during delivery. As most of the mothers were well, the series supported the important, emerging concept of a long incubation period for the AIDS agent before symptoms appear.

By the end of 1982, the CDC reported a total of 788 AIDS cases, 95% from one of four identified risk groups – homosexual men, heterosexual IV drug users, Haitians, and hemophiliacs – the “4H club,” as it was called with predictable stigmatizing results.²¹ Although transfusion of blood products in general did not make the list of specified risk situations, the hemophiliac cases and the baby who developed AIDS after a platelet transfusion from a man who subsequently died of AIDS were considered important, confirmatory evidence that the AIDS agent was blood-borne and could be transmitted by transfusion of blood and blood products. Official meetings were initiated with the blood services community to address this issue. Transmission from mother-to-child was not considered a confirmed risk group at that time.

The disease pattern changed dramatically in the first week of 1983 with a resulting major shift in the scientific and public response when the CDC reported AIDS in two women who had developed cellular immunodeficiency with no other risk factors except long-term sexual relationships with partners who had AIDS. AIDS had been diagnosed in an additional 41 previously healthy women who were in no other identified risk category: four of these women had steady sexual partners who were IV drug users.^{22,23} It was suddenly and alarmingly clear that the unidentified AIDS agent could be transmitted by heterosexual sex.

And then there were the children. After the original report at the end of 1982, two more series reported AIDS cases in infants and young children.^{24,25} All were small at birth and had severe growth failure with lymphadenopathy, hepato-splenomegaly (enlarged liver and spleen) and recurrent infections with rare organisms, associated with profound cell-mediated immunodeficiency. In each case, at least one parent had AIDS or a recognized high-risk condition for AIDS. At the time of the report, 27% of the children had already died.

An additional risk factor was confirmed by a national case-control study which compared 50 male homosexuals with AIDS to 120 matched healthy male homosexual controls, all volunteer research subjects from clinics in New York City, San Francisco, Los Angeles, or Atlanta. The two groups were interviewed and their responses to a wide array of personal and socio-demographic questions were recorded. The most significant finding was a striking difference in the number of sexual partners: the AIDS patients had a median of 68 partners in the last 12 months compared with 35 for controls. The number of sex partners correlated significantly with many other high-risk variables including meeting partners in bathhouses, previous history of syphilis, and use of nitrite inhalants.²⁶ Increased AIDS risk with multiple partners suggesting increased risk with increased exposure had emerged in other studies, but it had never been clarified as specifically as it was here.

Looking forward just 18 months from that first report in July 1981, that small case series sounded the alarm on a new epidemic caused by an unidentified agent

that decimated the immune system. The pathogen that caused AIDS was carried in body fluids and was transmitted sexually and through the blood. Multiple high-risk groups had been defined: homosexual males (especially those with multiple partners); heterosexual IV drug users; women whose sex partners had or were at high risk for AIDS, i.e., bisexual males or IV drug users; hemophiliacs who had received multiple clotting factor infusions; infants born to mothers who had or were at high risk for AIDS; and recipients of infected blood transfusions. (Haitian immigrants were also identified as a high-risk group and resolution of this putative etiology – described later in this chapter – would take several more years; unfortunately, the stigmatizing association of AIDS with Haitian heritage persisted for many years beyond that.) For all intents and purposes, AIDS was a uniformly fatal diagnosis: the reported mortality rate was at least 50%, but the death rate continued to rise with time from the original identifying illness – the average survival time after the diagnosis of AIDS was only between 9.5 and 22 months. Most worrisome was evidence of a prolonged asymptomatic but contagious carrier state that suggested the number of potentially infected patients far exceeded current reports. In addition, the possibility that the virus had contaminated the blood supply indicated a large new group of individuals at high risk. AIDS was a rapidly expanding epidemic, without an identified cause and with no effective treatment.

To this time, the general public had primarily seen AIDS as a mystery disease of gay men and drug addicts chased by epidemiologists in relative obscurity. With spread to women, babies and healthy people receiving routine blood transfusions, AIDS was suddenly a focus for the mainstream media and a cause of mounting public concern. At that time, the field of medicine was enjoying a genuine sense of accomplishment. In addition to the dramatic progress made in the development of antibiotics for treatment of infectious diseases, the twentieth century had seen major advances in almost every other area of medicine including development of vaccines against diphtheria, whooping cough, tetanus, yellow fever, and polio. Insulin therapy for diabetes was discovered, transforming this previously fatal disease. The heart–lung machine had been invented allowing routine open-heart surgery. Computed tomography (CT) scanning and magnetic resonance imaging (MRI) provided amazingly detailed views of the human body in health and disease. Kidney, liver, lung, and heart transplants were successfully performed. Against this backdrop, the emergence of a new, fatal epidemic was an unanticipated and unwelcome surprise, and a disease that was transmitted sexually and was especially common in promiscuous homosexuals was especially unwelcome at a time when the sexual revolution that began in the 1960s had only just started to make the possibility of sex outside of traditional heterosexual, married relationships acceptable.

It is hard to describe the terror that arose when AIDS was shown to potentially infect the whole population. With no identified cause and no treatment, the specter of the disease hung over the American population, fueled by media reports of seemingly random infections. Part of the rising public concern about AIDS was related to increasing media coverage, exemplified by the continuous 24-hour news

reporting launched by CNN in 1980, just as the epidemic was beginning.²⁷ A complete CNN news cycle consisted of the media reporting on some event, followed by reporting on public and other reactions to that report. News stories were presented as continuous news with constant updating, a major contrast with the previous day-by-day pace of the cycle of daily newspapers and scheduled TV news broadcasts. With spread to heterosexuals, even sporadic AIDS cases received intense, ongoing media coverage. The obvious limits of medical knowledge also fueled fear. When the epidemic began, even understanding of immune compromise was relatively limited, obtained primarily from experience with patients receiving drugs to suppress the body's natural immune response after organ transplant or as part of the reaction to cancer chemotherapy. AIDS appeared to be uniformly fatal, often in a very short time. Media coverage often fixated on stories that sensationalized the spread of the disease. "AIDS: Fatal, Incurable, and Spreading" read a typical headline from a cover of *People* magazine. The article began,

In recent months doctors have reported alarming signs that acquired immune deficiency syndrome (AIDS), the terrible, incurable disease that has ravaged the homosexual community for four years, now poses a growing threat to heterosexuals. ... 500,000 to 1 million Americans are carrying the virus that produces AIDS. About 10 percent will develop the disease over five years, doctors say; meanwhile they may transmit the virus, which has a latency period of three to five years, to their sexual partners ...²⁸

At the time, *People* had a weekly circulation of 2.8 million subscribers, so the potential impact of stories like this was substantial.

Discovery of the Human Immunodeficiency Virus

Two years into the epidemic, basic research lagged well behind the epidemiologic findings. This was not for lack of effort on the part of the CDC – as early as the fall of 1981 when there had been only a handful of reported cases, James Curran, Director of the newly created Task Force on Kaposi's Sarcoma and Opportunistic Infections at the CDC, met with a group of National Institutes of Health (NIH) researchers to describe what was known about this new disease and to outline what he felt were important research questions. There was no response. A year later he returned armed with specific information about the new, unidentified agent carried in body fluids and transmitted sexually and through the blood, that caused severe, fatal immunodeficiency focused on T-lymphocytes.²⁹ That combination of descriptors caught the attention of Robert Gallo, an established scientist at the NIH, who had spent the last 20 years studying retroviruses as a potential cause of malignancy in humans.

Remember, all viruses have a very simple structure with a core genome carrying genetic material, either RNA or DNA, inside a protein coat. In the vast majority of viruses, the genetic material is RNA. Reverse transcribing viruses

or retroviruses are a special subset: they have an RNA genome but use a DNA intermediate to replicate. Retroviruses had been discovered in the early 1900s and subsequently been shown to be RNA viruses that induced cancer in birds and mammals, but it was not until the enzyme reverse transcriptase was identified in 1970 that the process by which retroviruses turned viral RNA strands into DNA was understood.^{30,31}

Working with his own team of scientists, Gallo had identified a factor that promoted growth of T-cell lymphocytes; the first identified cytokine, this was originally called T-cell growth factor, but it is now known as interleukin-2 or IL-2. Using IL-2, Gallo's team had just isolated human T-cell leukemia virus (HTLV-1) in 1981 – the first identified human retrovirus. HTLV-1 was subsequently shown to be the cause of adult T-cell leukemia, a very common form of leukemia in Japan.³² The retrovirus HTLV-1 attacks T-lymphocytes and is transmitted from one person to another through the blood, by sex and *in utero* from mother to child.

A virus that attacked the T-lymphocytes of the immune system and was transmitted by body fluids sounded like an HTLV-like retrovirus to Gallo and he immediately began to explore the idea that some version of his newly discovered virus might be the cause of AIDS. At the same time, Max Essex, a Harvard researcher was exploring a potential role for feline leukemia virus, another retrovirus that attacks the immune system of cats. Searching for a retrovirus as the cause of AIDS proved to be a serendipitous first step that arose from conversation between these two scientists.²⁹

Gallo's laboratory was well prepared for this investigation after their years of experience culturing and growing T-cells in the process of identifying HTLV-1 and subsequently an additional retrovirus, HTLV-2. By May 1982, the laboratory had begun trying to identify a retrovirus in the blood of AIDS patients. Meanwhile, Luc Montagnier, a French virologist at the Pasteur Institute, was studying the lymph nodes of patients with AIDS. In January 1983, his laboratory identified reverse transcriptase enzyme activity in lymph node cells from a gay man with generalized lymphadenopathy.³³ At that time, retroviruses were the only entity known to use reverse transcriptase – and the only retroviruses known to attack humans were HTLV-1 and HTLV-2.

Needless to say, Montagnier's findings appeared to confirm Gallo's hypothesis that the AIDS agent was an HTLV-related virus and all of his subsequent research focused on proving this. In the same issue of the journal *Science* where Montagnier's group reported their lymph node findings, the Gallo group reported they had isolated a virus from a patient with AIDS and "shown that it was related to the HTLV subgroup 1".³⁴

Despite Gallo's repeated assertions, however, he was never able to prove that an HTLV-related virus was the cause of AIDS.³⁵ Instead, in September 1983 at a meeting of retrovirologists, it was Montagnier who reported that his group had isolated a virus from five pre-AIDS patients and three patients with AIDS. He called the virus "LAV" for "lymphadenopathy-associated virus" and reported two more important findings: LAV showed a specific affinity for CD4 T-cells; and detailed

analysis showed that it was not a variant of the HTLV group, but rather a member of the lentivirus family, a retrovirus subgroup.^{36,37} By the time the Pasteur group published these findings in April 1984, they had also shown that T-lymphocytes were the receptor for LAV and had isolated LAV from the French blood bank supply.^{38,39}

Over the next year, an increasingly acrimonious competition between Montagnier and Gallo, LAV vs. HTLV-III, played out until ultimately, the two viruses were shown to be identical by nucleotide sequencing and they were both renamed the human immunodeficiency virus – HIV.^{40,41}

Along the way, the Gallo group made critical contributions. They discovered how to grow HIV continuously in permanent culture – this allowed development of an accurate and sensitive blood test to detect antibodies against HIV which could be used to confirm infection with the virus and screen donated blood. The ability to confirm infection definitively clarified the epidemiology of the illness and theoretically would allow the earliest possible introduction of treatment. While Luc Montagnier and his colleague Francoise Barre-Sinoussi won the Nobel Prize in Medicine in 2008 for their discovery of the virus that caused AIDS, exclusion of Robert Gallo is hard to understand given his many important contributions to knowledge of HIV and AIDS.⁴²

The Virus

Discovery of the human immunodeficiency virus proved to be only a small first step in understanding the complex immuno-pathophysiology of the virus and the acquired immune deficiency syndrome. From Montagnier's work, HIV was identified as a retrovirus, from the family Retroviridae – these are enveloped, icosahedral viruses which replicate by converting the RNA genome into a DNA intermediate using the enzyme reverse transcriptase; the DNA intermediate is then converted to double-stranded DNA.⁴³

The new virus causing immune deficiency in humans was identified as a Lentivirus, a subgroup of the Retroviridae family which produces chronic and ultimately fatal disease in mammals after a long incubation period (Figure 6.1).⁴⁴ There are five serogroups based on the vertebrate hosts they infect. The main difference between lentiviruses and standard retroviruses is that lentiviruses are capable of infecting both non-dividing and actively dividing cell types, while standard retroviruses can only infect actively dividing cells. Lentiviruses are also known to have high mutation and recombination rates, major factors in the future struggle to identify effective treatment.

In 1986, a different lentivirus was isolated from West African patients with AIDS.⁴⁷ The genomic organization was found to be very similar to HIV and the two viruses subsequently became known as HIV-1 and HIV-2. HIV-1 is responsible for the majority of all human immunodeficiency virus infections, but HIV-2 causes a significant minority of cases, primarily in West Africa. Infection with either HIV-1 or HIV-2 will progress to AIDS if untreated, but the rate of progress is much

slower with HIV-2. HIV-1 as the cause of an ongoing global pandemic is the focus of this chapter.

Negative-staining electron microscopy shows HIV-1 and HIV-2 to be small, roughly spherical viruses, approximately 120 nm in diameter (Figure 6.1). Both are encapsulated viruses which contain a conical capsid enclosing the RNA genome plus all the enzymes essential for formation of new viruses.⁴⁸ Nucleotide sequencing was accomplished by 1985 and since that time, increasingly sophisticated molecular genetic techniques including cryo-electron microscopy and tomography, and all-atom large-scale molecular dynamic simulations have revealed that HIV is a very complex virus.^{45,46} The HIV envelope includes glycoproteins displayed on the surface of the virus as spikes which are used for host cell entry. The envelope spikes bind to the host target cell CD4+ receptor and a chemokine co-receptor, typically CXCR4 or CCR5; this process anchors HIV to the host cell. The viral and host membranes fuse, the viral capsid enters the cell, and the core genome dissolves, releasing the HIV RNA copies. Reverse transcriptase then converts the single-stranded RNA to double-stranded DNA, using cellular nucleotides as the building blocks for DNA synthesis. The HIV DNA complex migrates inside the host nucleus and integrates into the host DNA, forming the HIV/DNA provirus. The HIV provirus remains part of the host DNA forever, perceived by the cell as normal host cellular DNA. Cellular enzymes can then transcribe the proviral DNA into messenger and genomic RNA which are exported out of the nucleus into the cytoplasm and reassembled as mature HIV virions, ready to infect other cells (Figure 6.1).^{49–52} Despite intensive study for more than two decades and increasingly detailed knowledge of the virus, complete understanding of the HIV infection process remains the goal of ongoing research.⁵³

Like all lentiviruses, HIV populations have enormous genetic variation revealed by molecular phylogenetic studies. HIV is reported to have the highest recorded biological mutation rate currently known to science. Point mutations due to base substitutions occur very frequently, primarily because – as in all RNA viruses – the absence of proofreading makes the process of RNA synthesis error-prone. This results in a baseline spontaneous mutation rate of at least 1% per year. Within a single infected individual, the virus evolves extremely frequently and rapidly, resulting in multiple mutant versions of the virus.⁵⁴ As with the influenza virus, there is a second important mechanism for genetic variation: recombination – the exchange of entire gene sequences at unselected positions – occurs when a target cell is infected with different HIV subtypes. Recombination of HIV-1 subtypes is considered a driving force for its diversity worldwide, responsible for frequent and important genetic variation in the virus; approximately 1 in 400 newly produced HIV virus particles is a recombinant virus containing combined genetic material. Such a recombinant is called a unique recombinant form (URF). If an inter-subtype recombinant virus succeeds in being transmitted to many people, it becomes one of the circulating strains in the HIV epidemic and is classified as a “circulating recombinant form (CRF)”;

at least 89 different CRFs have been identified.⁵⁵

Genetic variability has resulted in multiple HIV-1 variants which are classified into four major phylogenetic groups: M, N, O, and P. Group M is responsible for pandemic HIV-1 infection and is further subdivided into 10 recognized, genetically distinct subtypes, labelled A to K. The dominant HIV-1 subtype in the Americas, Western Europe and Australasia is subtype B and the majority of clinical research has been conducted in populations where subtype B predominates. Globally, nearly 50% of all people living with HIV have subtype C, which is very common in high-prevalence HIV/AIDS areas like Africa.⁵⁶ HIV-2 has the same high degree of genetic diversity as HIV-1 with at least seven HIV-2 subtypes.⁵⁷ To this time, there is no evidence that any HIV-1 or HIV-2 subtype is more infectious than others. Population mixing means geographical patterns in the distribution of subtypes are continually changing. So far, tests to diagnose HIV and monitor the level of virus in the body are sensitive to the full range of subtypes. The extensive and ongoing genetic heterogeneity of HIV-1 is a major reason for rapid development of drug resistance and for problems with vaccine development.

The chemokine receptor CCR5 is a key player in HIV infection due to its role as the co-receptor for virus entry into CD4+ lymphocytes. A rare, naturally occurring nucleotide deletion in the CCR5 gene has been found to be strongly associated with resistance to HIV infection despite frequent sexual exposure to the virus, as well as long-term control of HIV infection in a subset of HIV seropositive people. These individuals are called long-term non-progressors and have most often been shown to have a rare homozygous deletion of CCR5. This allele was found in 8% of white gay men enrolled in the Multicenter AIDS Cohort Study, but in no participants of African or Asian descent.⁵⁹ These “natural” immunities have prompted strategies aimed at achieving anti-HIV humoral responses through CCR5 targeting.^{58,59} Specific patterns of the human leukocyte antigen (HLA) system have also been shown to delay the progression of HIV infection. It is likely that other, as yet undiscovered genetic correlates of race, ethnicity, and gender that confer resistance or susceptibility will explain some of the variability in HIV infection and disease progression rates.⁶⁰

A final, critical factor in HIV infectivity was first recognized almost 20 years ago – but also 20 years after the first AIDS cases appeared – when HIV-infected individuals were found to harbor hidden reservoirs of HIV-infected cells. These are sites that allow persistence of the virus in a latent, non-replicating state. The reservoir for HIV is primarily in a subset of long-lived CD4+ T-lymphocytes called resting memory cells that are widely distributed throughout the body, primarily in secondary lymph nodes that line the GI tract but also in the spleen and in the brain. The reservoir is established within the first few days after HIV infection; after initiation of long-term antiviral treatment, there is a fairly rapid initial decline in the size of the reservoir, but subsequently, there is only a very slow decline over the lifetime of infected individuals. HIV reservoirs explain the near impossibility of complete HIV eradication to this time. Ongoing research is focused on developing methods to reverse latency and then rapidly eliminate the reactivated virus population.⁶¹

The Disease: HIV Infection and the Acquired Immune Deficiency Syndrome

Identifying the human immunodeficiency virus and understanding its unique characteristics dramatically clarified critical components in the pathophysiology of the disease and the course of the epidemic: first, HIV infection is difficult to acquire: it can only be contracted through direct mucous membrane or blood contact with body fluids – genital fluids, blood or breast milk – of an infected person. HIV is very slow-acting: the extremely long incubation period of the virus is a critical factor in understanding the disease. And, HIV is inexorable: without treatment, the virus progressively destroys the immune system in almost every infected individual, leading to overwhelming opportunistic infections caused by bacteria and fungi, and/or opportunistic neoplasms related to infection with oncoviruses.

HIV is transmitted primarily via unprotected sexual intercourse including vaginal, anal and (very rarely) oral sex; contaminated hypodermic needles in IV drug users; and from mother to child during pregnancy, delivery, and/or breastfeeding; infection via contaminated blood products has almost completely disappeared. The principal targets of invading HIV are the cells of the immune system, particularly CD4+ T cells, whose role is to clear foreign pathogens from the body. After entering a host cell, the virus begins a relentless process of replication during which the immune system of the host organism is progressively destroyed. The human immunodeficiency virus produces up to 10 billion new viral particles and destroys up to 2 billion CD4+ cells per day.⁶²

There are three stages of HIV infection: acute infection, clinical latency, and AIDS, the acquired immunodeficiency syndrome as shown in Figure 6.2. Acute HIV infection is characterized by a non-specific flu-like illness with fever, sore throat, large tender lymph nodes and rash. Much less frequently, there are sores in the mouth and on the genitalia, and GI or neurologic symptoms. These initial symptoms are transient, only one or two weeks. During this time, immune function is severely compromised and viral counts are extremely high. Due to their mild and non-specific character, these symptoms are often not recognized as signs of HIV infection.⁶³

The initial symptoms are then followed by a stage called clinical latency, asymptomatic HIV, or chronic HIV which lasts from 3 to over 20(!) years. Recognition of the long duration of the incubation period was one of the most startling realizations of the early AIDS epidemic. The original AIDS cases with opportunistic infections presented acutely with overwhelming illness so the question of a significant incubation period for the unknown transmission agent did not arise. Recognition that homosexuals without symptoms already had abnormalities of immune function first introduced the idea of an AIDS prodrome.^{9,16} But it was from the transfusion history of individuals with AIDS who were infected by receiving contaminated blood products that a specific date of infection could be identified and the existence of a prolonged incubation period was verified.⁶⁴ Ultimately, follow-up of cohorts of individuals at high risk for HIV infection established an average incubation period

of approximately 10 years.^{65,66} Older age at infection was identified as a significant factor accelerating disease progression based on studies of hemophiliacs.⁶⁷

During this period of viral incubation and clinical latency, viral multiplication and CD4⁺ cell destruction continue while the individual remains asymptomatic – CD4 lymphocyte counts decline by an average of 50–75 cells/ μ l/year.⁶⁴ Historically, the WHO used absolute CD4 lymphocyte count to categorize disease progression:

- Stage 0: The time between a negative HIV test followed in less than 180 days by a positive test
- Stage 1: Early disease; no AIDS defining conditions; CD4 count $\geq$ 500 cells/ μ l
- Stage 2: Mid-stage disease; no AIDS defining conditions; CD4 count 200–500 cells/ μ l
- Stage 3: Advanced disease: AIDS-defining condition or CD4 count 50–200 cells/ μ l. AIDS diagnosis per CDC 1993 revised definition.
- End-Stage: CD4 count < 50cells/ μ l.

Since approximately 1999, assays that measure the number of circulating viral RNA copies in the blood – the viral load – have also been used to monitor therapy. CD4 cell count and viral load together are used to estimate prognosis, but viral load is the single most powerful predictor of progression from HIV infection to AIDS and of AIDS progression to a terminal stage, with or without treatment.^{68,69} Successful treatment aims for a viral load “below the level of detection” (< 50 copies/ml).

In the absence of specific treatment, 98% of those infected with HIV will develop full-blown AIDS by 10 years and die within 20 years post infection. During this entire time, testing for HIV-1 RNA can be measured in the plasma and tests for HIV are positive.⁶⁸ At the end of the latency stage, patients may experience symptoms like recurrent fever, weight loss, gastrointestinal symptoms like chronic diarrhea, and muscle pain. Between 50% and 70% of people develop a prodrome of generalized, unexplained, non-painful enlargement of more than one group of lymph nodes lasting 3–6 months, as recognized by epidemiologists in the first years of the AIDS epidemic.¹⁶ The onset of symptoms – and therefore the shift in diagnosis from HIV infection to AIDS – reflects near-total destruction of the immune system. The timeline of HIV infection is shown in Figure 6.2.

AIDS is officially diagnosed when patients develop opportunistic infections or HIV-related malignancies that are normally prevented by the body’s immune system – these are labelled AIDS-defining events. Development of AIDS is also defined in terms of immune compromise using a CD4⁺ T cell count below 200 cells per μ l without clinical symptoms. Those patients who presented as the first AIDS cases in 1981 were in this late stage at the time they were first seen. Twenty per cent of AIDS patients will develop progressive severe weight loss with chronic diarrhea called HIV wasting syndrome, the equivalent of the so-called “slim disease” seen in Africa. Opportunistic infections include a wide array of pathogens but especially pneumocystis and other severe fungal infections in North America and tuberculosis in Africa.⁷⁰ This brief statement in no way describes the severity of the

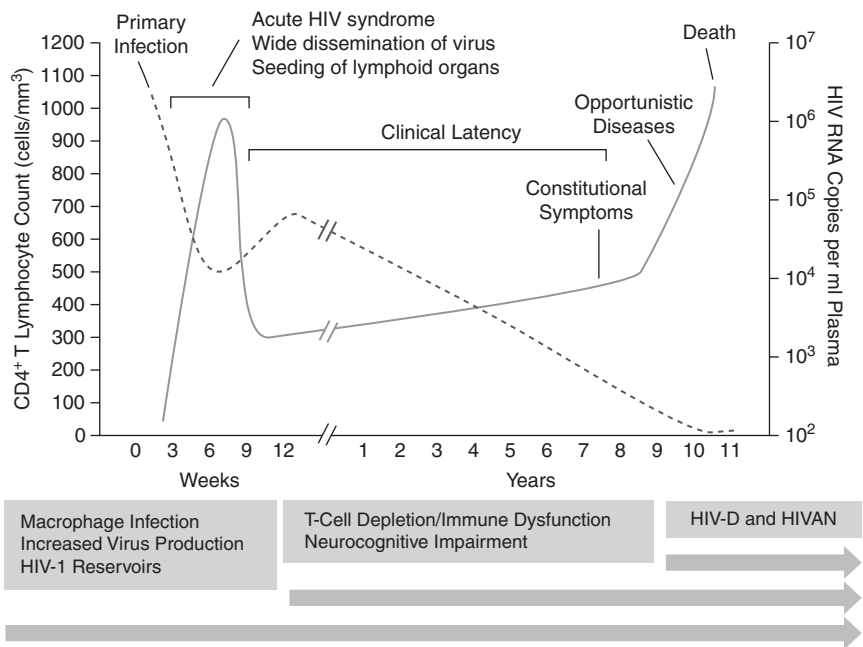


FIGURE 6.2 Timeline of CD4 T-cell and viral-load changes over time in untreated human immunodeficiency virus (HIV) infection.

Source: Courtesy of Wikipedia (based on an original from Pantaleo et al. 1993).

symptoms or the degree of suffering associated with full-blown AIDS: pneumonia with pneumocystis is often so overwhelming that patients require respirator support and even with intensive care and aggressive antifungal treatment, acute mortality can still be as high as 40%.⁶⁹ Fungal infection of the mouth and esophagus is very common in late stage HIV(+) individuals; the infection is usually secondary to the yeast *Candida albicans* and can cause such severe pain and swallowing difficulty that hospitalization for hydration and pain control is necessary.⁷¹ And alas, surviving one severe opportunistic infection does not prevent a new – and often ultimately fatal – infection in the near future.

The time course of the CD4+ T-cell count and RNA viral load from the time of HIV infection are shown in Figure 6.2. During the very prolonged latency period lasting 3–20 years, the CD4+ T-cell count (and therefore immune competence) progressively decreases and viral load (HIV RNA copies) increases but patients are primarily asymptomatic. AIDS-defining events only occur with critical lowering of the CD4+ lymphocyte count.

People with HIV infection are also at increased risk for viral-induced malignancy, especially Kaposi’s sarcoma, non-B-cell lymphoma (most often primary central nervous system lymphoma), and invasive cervical cancer. Just as originally reported, KS is the most common HIV-related cancer, occurring in 10–20%

of untreated people with HIV infection; it is most often related to infection with the lymphotropic herpes virus, human herpesvirus 8.⁷² The second most common HIV-related cancer is lymphoma, with the increased risk related to multiple factors, including the transforming properties of the retrovirus itself, the immunosuppression that results from the disease, and opportunistic infections with lymphotropic herpes viruses such as Epstein–Barr virus and, again, human herpes virus 8. The heterogeneity in the pathogenesis of lymphoma in HIV-infected patients is reflected in the variety of morphological subtypes. Lymphoma was the cause of death in nearly 16% of untreated people with AIDS and was the initial sign of AIDS in 3–4% of patients in the early years of the epidemic.⁷³ Cervical cancer is related to infection with the human papilloma virus (HPV) and is the most common AIDS-related malignancy in women.⁷⁴ These three malignancies are considered to be opportunistic neoplasms and are AIDS-defining cancers in HIV-infected patients.

Host genetics have been shown to be significant cofactors in HIV infection and disease progression, potentially explaining differing rates of infection in different demographic, racial, ethnic, and gender groups. As previously described, a minority of white HIV(+) individuals show very delayed progression from HIV infection to AIDS with stable CD4+ counts and low RNA virus loads for many years – perhaps indefinitely – due to a rare homozygous deletion of CCR5, the co-receptor for HIV entry into CD4+ lymphocytes. These individuals are also markedly resistant to HIV-1 infection.^{58,59} Even heterozygotes for CCR5 have significantly less rapidly progressive disease. Of equal importance in determining rates of HIV infection and disease progression but much harder to measure and address are societal factors like poverty, racism, structural violence, homophobia, lack of knowledge and delayed/limited access to healthcare.

The immune response to foreign antigens is regulated by the HLA system, which is defined by major histocompatibility-complex genes. Another small subset of patients have specific HLA subtypes which are associated with HIV control.⁶⁰ By applying molecular and serologic techniques to HIV(+) individuals, HLA combination gene profiles were developed and analyzed statistically in a cohort of HIV(+) men and validated in a second unrelated cohort. In the validation cohort, specific profiles discriminated as much as a sixfold difference between groups in time from infection to development of AIDS.⁷⁵ Patients with a high HLA score remained AIDS-free for a median of 10.7 years compared with those with a low HLA score, who developed AIDS at a median of 5.2 years after seroconversion.⁷⁶

Testing for HIV Infection

The ability to confirm HIV infection was a critical milestone in the AIDS epidemic. Individuals infected with HIV develop specific antibodies within 3–12 weeks of the initial infection and all of the early tests focused on antibody detection. The first test – developed by the Gallo team – used blood and was known as an enzyme-linked immunosorbent assay or ELISA test. It was approved for use in 1985. This early test was designed to screen donated blood for possible infection. Although

only 142 Americans were known to have contracted AIDS from blood transfusions at that time, public fear of contaminated blood was running high so blood donation centers began using the test immediately in April 1985. By the end of July, only 3 months later, the blood supply was declared free of HIV.⁷⁷

This first-generation test was not designed for testing of individuals because it had a high false positive rate: this was not a problem for blood banks, but it was definitely a major concern for frightened individuals. In addition, testing for HIV was associated with the very real threat of stigma and discrimination – being tested at all could be interpreted as a sign of belonging to one of the known high-risk groups which included homosexuals and IV drug users. With pressure to provide accurate testing for individual people, protocols were developed including retesting positive results with an additional procedure to improve accuracy before declaring test results positive. By March 1986, the US government had issued a recommendation that people in all “high-risk groups” seek periodic testing to determine if they were infected with the virus. Laws requiring specific informed consent for HIV testing were developed with mandatory before-and-after counseling and because of privacy concerns, HIV test results were excluded from laboratory and hospital systems.⁷⁸

Since that time, a series of new testing methods have been developed, including the addition of a recombinant antigen. With each new generation of screening tests, the specificity has improved and the negative testing window post-infection has decreased. The most recent testing iteration was launched in 2015 and uses multiplex analysis to detect both HIV antibody and the selected HIV-1 antigen; the negative window has been reduced to 2 weeks. Independent testing reports 100% sensitivity and 99.5% specificity with this test. Rapid HIV assays for use in situations where results are needed immediately have also been developed using blood, serum or saliva. There are “at home” versions of these tests which have been shown to have 100% sensitivity and up to 96% specificity with results in as little as 30 minutes. In the window period between infection and the development of antibodies, accurate testing requires RNA tests which can detect the virus directly beginning about 10 days after infection. Positive results obtained by either antibody or polymerase chain reaction (PCR) testing are confirmed by repeat testing. Over time, HIV testing has become more accepted and screening results are treated like other test results, included in laboratory and hospital records.⁷⁷

Since 2006, the CDC has recommended routine, provider-initiated HIV screening for all adults with specific recommendations for adolescents and pregnant women.⁷⁸ Since 2007, WHO and UNAIDS guidance has also been given for provider-initiated HIV testing and counselling.^{79,80} However, not everyone is following these recommendations. In 2014 when an estimated 1.1 million people in the US were living with HIV, 15% were not diagnosed. Even more concerning, among Americans aged 13–24 with HIV infection, an estimated 44%(!) did not know their diagnosis. Thirty per cent of new HIV infections were transmitted by people living with undiagnosed HIV.⁸¹ Globally, the WHO estimated in 2016 that of an estimated 36.7 million people living with HIV, 30% did not know that they were infected with the virus.⁸²

Prevention, Treatment and Treatment as Prevention: USA

By the mid-1980s, the AIDS epidemic in the United States had seen dramatic progress with description of the epidemiology of the disease, identification of the causative virus, understanding of the disease pathophysiology and development of a test to diagnose infection. However, a diagnosis of AIDS was still, essentially, a death sentence with 16,301 known deaths due to AIDS by 1986. The development of effective methods for prevention and treatment was the dramatic story of the next two decades ...

1. Prevention

In the early years when there was no treatment, AIDS in the United States was exclusively associated with homosexuality, drug abuse, sexual transmission and death – AIDS patients were essentially marginalized and ignored. Pictures of skeletal figures with disfiguring skin lesions fueled the prevalent public attitudes of fear, denial, and discrimination. At least partially because knowledge was so limited, American health organizations at first declined to supply any information at all. Even healthcare workers at both the national and community levels were reluctant to care for patients with AIDS. In this atmosphere, the first attempts at prevention arose from within the gay community where the forefront of early cases appeared. In 1982, Michael Callen and Richard Berkowitz, two gay men living with AIDS in New York City, published *How to Have Sex in an Epidemic*, which presented the concept that condoms could be used to protect against becoming infected and to prevent spreading the disease. That same year, the Sisters of Perpetual Indulgence, a gay activist group in San Francisco, self-published a pamphlet also promoting condom use to prevent infection – these were the first known descriptions of “safe sex” and a giant step forward in HIV prevention.⁸³ For many years, these two small books were the only available information about prevention of AIDS.⁸⁴ Eventually, multiple HIV seroconversion studies showed that latex condoms are 90–95% effective when used consistently – validating the original, simple and clear “safe sex” message in these two pamphlets.⁸⁵

In March 1983, the CDC issued its first recommendations for prevention of AIDS:⁸⁶

1. Sexual contact should be avoided with persons known or suspected to have AIDS. Members of high-risk groups should be aware that multiple sexual partners increase the probability of developing AIDS.
2. As a temporary measure, members of groups at increased risk for AIDS should refrain from donating plasma and/or blood. This recommendation includes all individuals belonging to such groups, even though many individuals are at little risk of AIDS. Centers collecting plasma and/

or blood should inform potential donors of this recommendation. The Food and Drug Administration (FDA) is preparing new recommendations for manufacturers of plasma derivatives and for establishments collecting plasma or blood. This is an interim measure to protect recipients of blood products and blood until specific laboratory tests are available.

3. Studies should be conducted to evaluate screening procedures for their effectiveness in identifying and excluding plasma and blood with a high probability of transmitting AIDS. These procedures should include specific laboratory tests as well as careful histories and physical examinations.
4. Physicians should adhere strictly to medical indications for transfusions, and autologous blood transfusions are encouraged.
5. Work should continue toward development of safer blood products for use by hemophilia patients. The National Hemophilia Foundation has made specific recommendations for management of patients with hemophilia.

In retrospect, these were extremely conservative recommendations given the gravity of the situation: since 1979, the number of patients diagnosed by the strict CDC definition had doubled every 6 months. Approximately 50 new cases of AIDS were being registered each week by the CDC and more than 2000 cases had been reported by the end of 1983. Despite this exponential increase, abstinence was the only recommendation for individuals “known or suspected to have AIDS” as was “awareness that multiple sexual partners increased the probability of developing AIDS”; there was no mention of condoms. Individuals from groups at increased risk for AIDS – not named – were asked to not donate blood and blood banks were taxed with communicating this message, but there was no recommendation for blood donation centers to question potential donors themselves. With no public education program, it was unclear how this information would reach the groups that needed it. Development of AIDS screening tests was recommended – who could disagree with that? – and doctors were asked to limit blood transfusions as much as possible; patients were encouraged to donate their own blood prior to surgical procedures with infusion of the donated blood as needed. Hemophiliacs were referred to hematology recommendations developed specifically for them.⁸⁶ There was a strong sense of handwringing with no practical, evidence-based guidelines for prevention.

As described, the original test for HIV infection was released in 1985. Its limitations aside, the test was greeted enthusiastically by blood banks, healthcare providers and frightened individuals in high-risk groups. Unfortunately, testing for HIV was potentially dangerous because being tested at all could be interpreted as a sign of being gay or an IV drug user. By March 1986, the CDC had issued a recommendation that people in all “high-risk groups seek periodic testing” to determine if they were infected with the virus. HIV testing required specific informed consent and test results were excluded from laboratory and hospital records.⁷⁷

The first official public health response to the AIDS epidemic occurred in 1986 following years of silence during which federal funding for public health had been repeatedly cut, effectively limiting any potential response of agencies like the CDC or the NIH to the emerging threat. Open discrimination against people with AIDS was the common public attitude: they were routinely evicted from their homes, expelled from their classrooms, and fired from their jobs. As the crisis unfolded, many doctors and nurses openly proclaimed they would not treat a patient with AIDS because of personal risk and the obligation to protect their own families. The response of the government and of elected officials encouraged this marginalization and discrimination against AIDS patients. President Reagan did not even use the term AIDS in public until 1985, more than 4 years into the epidemic; by that time, there were more than 12,000 reported cases with 6000 deaths and AIDS had spread to every populated continent on the planet. Even then, he questioned the safety of casual contact, specifically opposing allowing children with AIDS to continue in school, something that had already been defined as safe by his own governmental medical experts.⁸⁷

For years, Reagan prevented his Surgeon General, C. Everett Koop, from speaking out about AIDS. In 1986 when Koop was finally allowed to address the epidemic, his *Surgeon General's Report on Acquired Immune Deficiency Syndrome* used clear, candid language to review the symptoms of the disease and its modes of transmission. The report stated explicitly that AIDS could not be spread casually, reassuring the public that children attending schools with HIV(+) students were safe. It called for a nationwide education campaign with emphasis on early sex education in schools, increased use of condoms, and voluntary HIV testing.⁸⁸ In 1988, Koop took the unprecedented action of mailing AIDS information directly to every US household, explicitly recommending the use of condoms as a highly effective defense against HIV infection. This report was a decisive advance, educating the public about how HIV is transmitted and the use of safe sex practices to prevent it. The Surgeon General helped redefine AIDS as a preventable disease that ultimately allowed the full integration of HIV(+) individuals into society.

Following Dr. Koop's lead, a national effort to educate the public about HIV and AIDS was launched in 1987 and the CDC created a comprehensive AIDS information resource, the CDC National AIDS Hotline and National AIDS Information Clearinghouse. Comprehensive school-based HIV education to inform and educate young people began in 1987, and funding for national, regional, and community-based organizations began in 1988. The first research on effective behavior interventions to reduce transmission of HIV among sex partners began in the mid-1980s. Ultimately, selected behavioral interventions, including school-based programs, peer-to-peer interventions, strategies that use parent-to-child communication and personalized risk-reduction strategies proved to be moderately effective in promoting behaviors that prevent HIV infection.⁸⁹

Over time, public knowledge about AIDS increased and attitudes improved in response to advocacy of groups like ACTUP and celebrities like Elizabeth Taylor and Elizabeth Glazer who campaigned for acceptance and treatment.⁸⁷ Taylor

founded The Elizabeth Taylor Foundation to provide support services for people with HIV/AIDS and prevention education for populations most in need. In 1991, Magic Johnson, arguably the most famous basketball player in the world at the time, announced that he was HIV-positive. His pre-season bombshell made headlines worldwide. Phil Wilson, head of the Black AIDS Institute, was the AIDS coordinator for the city of Los Angeles at the time. He says Johnson's announcement shut down his switchboard. "It was the single most powerful event at the time to raise awareness about AIDS in black America." Kenny Smith, then of the rival Houston Rockets said, "Before then, people were ostracized, in my estimation, for having the disease. Magic was the person, because his name reached far beyond sports, to make HIV acceptable, more a disease than a mark of shame." Johnson went on to establish the Magic Johnson Foundation, dedicated to AIDS-related research and outreach.⁹⁰ He has remained very involved in AIDS activism, especially education about the risk for heterosexuals and African Americans, launching the "I Stand with Magic" partnership to promote HIV testing and sustained treatment adherence for HIV-positive individuals at a meeting of the National Minority AIDS Council in 2006.⁹¹ Twenty-five years after the announcement that he was HIV-positive, *Rolling Stone* wrote,

... some moments truly transcend sports and shake the world. Great plays or broken records might resonate with fans, but there are usually only a handful of situations that can define a decade. We like to think that athletes do things that can change the world, but very few do. Earvin "Magic" Johnson's November 7th, 1991 announcement that he was HIV positive was one of those moments.⁹²

Celebrity activists like Taylor and Johnson highlighted injustice and prejudice against people with HIV/AIDS, demanded increased government resources to fight the disease, established private foundations to support research and treatment and accelerated the slow process of changing public attitudes about HIV/AIDS.

New HIV infections in the United States peaked at 150,000/year in the mid-1980s with a gradual subsequent decline. However, despite education and prevention efforts, there were 50,000 new cases every year from 1992 to 2015. Although the CDC still only recommends mandatory annual HIV testing for gay and bisexual men, they recommend screening for STDs and HIV every 3–6 months for individuals who have more than one partner or have had casual sex with people they don't know.

After observational studies suggested a potential benefit of male circumcision in preventing HIV infection, a randomized controlled trial was performed in heterosexual men in South Africa. After a mean follow-up of 18 months, the relative risk of HIV infection in the circumcised group was 0.40 – less than half – compared to the control group, an impressive 60% protection rate.^{93,94} Results of male circumcision show equivocal benefits in preventing homosexual acquisition of HIV.⁹⁵ Since 2007, WHO/UNAIDS has recommended male circumcision as an

efficacious intervention for HIV prevention in countries and regions with heterosexual epidemics, high HIV prevalence and low male circumcision prevalence. In 2014, the CDC recommended circumcision in male patients and in newborn males as effective prevention against infection with HIV and other STDs.⁹⁶

II. Treatment

In the early years, a diagnosis of AIDS was essentially a death sentence because patients presented very late in the course of the disease with overwhelming infections when the immune system had been essentially destroyed. The only available treatment was for the existing, often rampant, infections and most AIDS patients died within months of diagnosis. As the critical role of immune compromise was better understood, antiviral agents were prescribed, but at that time, these were few in number and experience in the context of a disease like AIDS was non-existent. Recognition that prophylactic antibiotics could reduce/prevent *Pneumocystis* pneumonia led to CDC guidelines, but not until 1989 with a revision in 1992.^{97,98}

Early clinical tests showed that a drug called azido-thymidine or zoluidine (AZT), which had been developed in the 1960s as an anticancer agent, slowed the progress of HIV in humans. At that time, the drug approval process in the US was extremely slow and as AZT was not approved, access was restricted to patients enrolled in clinical trials. Outraged by federal regulations and policies that slowed the development, testing and distribution of drugs to treat HIV/AIDS, activists and community-based organizations were galvanized to take action. Their public demonstrations ultimately helped change the way clinicians, researchers, drug companies, and local, state and national governments addressed the HIV/AIDS epidemic and, by extension, drugs to treat any disease.⁹⁹

(For more on this, see the Historic Perspective at the end of this chapter.)

Meanwhile, AZT had been shown to inhibit reverse transcriptase – the critical retrovirus enzyme – in a mouse retrovirus model and with its precise mode of action known, the drug could be studied in detail. A randomized clinical trial was begun and 6 months after initiation, only one member of the group receiving AZT had died, compared to 19 deaths in the control group. The trial was halted and AZT was approved as treatment for HIV and AIDS in 1987 – 6 years after the first cases appeared.¹⁰⁰ Although its arrival was greeted with great optimism, resistance to AZT was found to develop rapidly. In 1990, the second drug for the treatment of AIDS, dideoxyinosine (ddI), was made available to people with AIDS, even though only preliminary tests had been completed and one year later, a third drug, dideoxycytidine (ddC), was authorized by the FDA for use in patients intolerant of AZT.^{101,102}

AZT, ddI and ddC are all nucleoside analog reverse transcriptase inhibitors. After 1991, another new class of anti-HIV drugs, the non-nucleoside analog reverse transcriptase inhibitors, was developed – these are more quickly activated once inside the bloodstream. Next were protease inhibitors which prevent an already infected cell from producing more copies of HIV. Each of these drugs appeared to be partly

efficacious, with great variation in response between individuals. Despite this proliferation of drug options, the standard antiviral therapy for HIV-infected individuals between 1986 and 1995 for the most part remained treatment with a single drug. In 1992, the FDA approved the use of combination therapy with ddC and AZT for patients with advanced HIV infection and clinical or immunological deterioration, the first successful use of combination drug therapy for the treatment of AIDS.¹⁰³

Increased appreciation of the capacity of HIV for rapid mutation associated with development of drug resistance led to the emergence of combination therapy as a primary treatment approach, with drugs from two or more classes used simultaneously. This switch to combination therapy had dramatic effects because in most cases, the virus remained sensitive to at least one of the drugs used. When nucleoside analog drugs, the non-nucleoside analog drugs, and the protease inhibitors were used together, the combination was referred to as “highly active antiretroviral therapy” or HAART.¹⁰⁴ As shown in Figure 6.3, introduction of HAART in 1995 led to a dramatic reduction in deaths from AIDS in the United States, the first decrease in mortality since the epidemic began.

In addition to the dramatic decrease in death rates for all groups, the graph in Figure 6.3 also reveals chronic disparities between black and Hispanic individuals of either sex compared with whites. These differences reflect ongoing structural barriers including not just race/ethnicity but also poverty, limited or difficult access to health care, lack of HIV education, fear, and persistent stigma associated with homosexuality and/or drug use. Socio-economic barriers like these can result in delayed diagnosis and treatment initiation, and interruption and/or cessation of treatment, manifest as lower rates of linkage to care and viral suppression, and higher rates of death in race- and sex-defined, vulnerable populations.^{104–106}

Over time, particular combinations of drugs were shown to have the most dramatic effects, reducing the amount of virus in the blood and increasing the number of CD4+ cells. By the end of 1996, the number of Americans dying from AIDS had declined by 23% from the previous year, attributed primarily to the success of the new combination therapies. By the start of 1997, HAART combination therapy had become the standard of care for HIV-infected individuals with signs of significant immuno-suppression. New drugs have been added to the ART armamentarium over time, with integrase strand transfer inhibitor (INSTI)-based regimens now recommended as part of initial therapy for most people with HIV.

In all, the simultaneous treatment of people with HIV with different classes of antiviral drugs is the most significant scientific advance in the history of the AIDS epidemic.

Now almost 20 years after its introduction, combination antiviral therapy has demonstrated impressive, sustained ability to control progressive disease in AIDS patients. Along the way, treatment has evolved from the early “grueling regimens with high pill burden, inconvenient dosing, treatment-limiting toxicities, food and drug interactions, incomplete viral suppression and emergence of drug resistance to manageable one or two pill once daily regimens that can be initiated in early

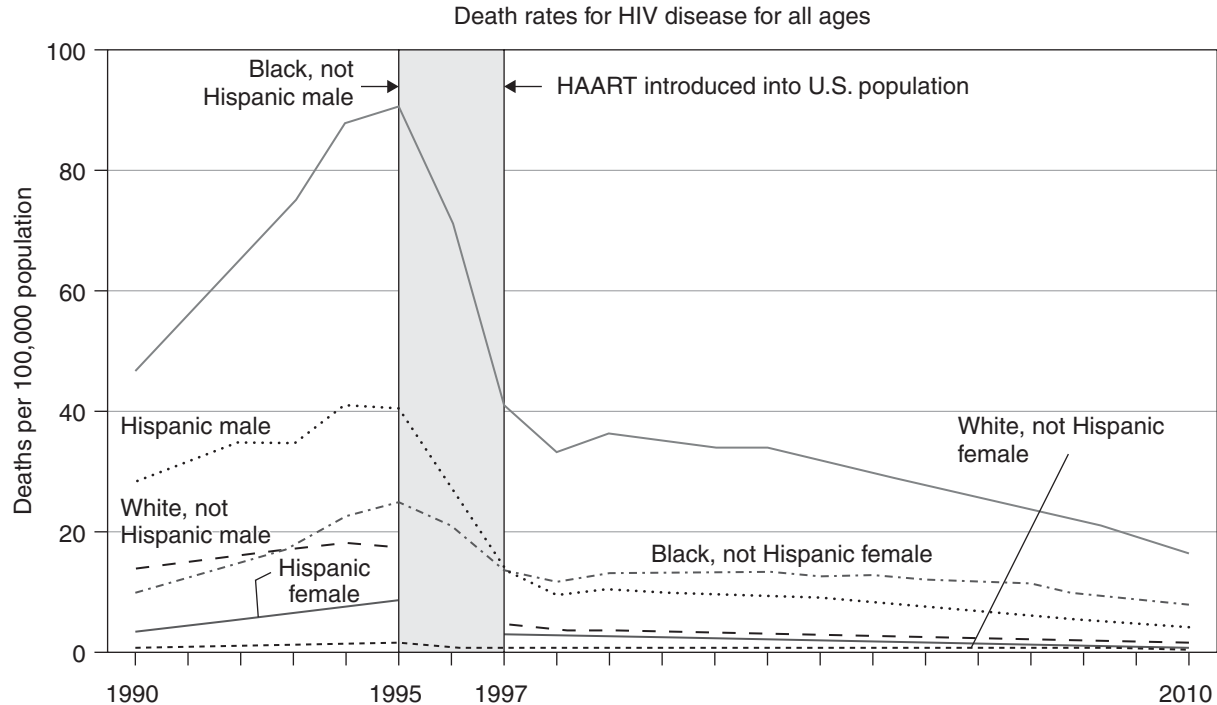


FIGURE 6.3 Death rate for HIV disease for individuals of all ages by race/ethnicity and gender after introduction of highly active antiretroviral therapy (HAART). This dramatic change was the first decrease in mortality since the epidemic began in 1981.

Source: Figure from CDC/National Center for Health Statistics, United States, 2013. (CDC.gov)

HIV disease and continued with control of viral replication over ... an individual's lifetime."¹⁰³

With the possible exception of two HIV(+) individuals who received stem cell transplants because of cancer, complete elimination, or "eradication," of HIV from an infected individual has never been achieved. Antiviral medications still allow full or partial resistance to develop with missed medication doses, irregular use, or incomplete doses, and cross-resistance is common so strict adherence to the prescribed drug regimen is necessary. Disparities in access to care persist in key affected populations. Nonetheless, the overall impact of combination antiretroviral therapy (cART or ART – the new acronyms for HAART) has been overwhelmingly positive.

Treatment as Prevention

With time and experience, the approach to initiation of antiretroviral treatment – cART/ART – evolved. Measuring the viral load of circulating viral RNA copies in the blood was used to monitor therapy, and CD4 cell count and viral load together were shown to provide the most accurate prognosis of future outcomes. Successful treatment often led to a viral load "below the level of detection" or < 50 viral copies/ml, indicating that the concentration of HIV in the blood was very low. Based on observations that rates of HIV transmission paralleled the viral load, the risk of infecting others was thought to potentially be very low in this situation.

Landmark research addressed this by investigating initiation of ART in healthy HIV(+) people with CD4 counts above 350 cells per cubic millimeter – the internationally recognized level below which ART initiation was recommended at that time. This was an international multi-center trial which included sites in the United States, Brazil, Thailand, India and multiple countries in Africa with two very important results: for HIV(–) partners, preventive ART significantly limited transmission of the virus by 96%. In the HIV(+) individual, early ART preserved CD4+ counts, delayed progression to AIDS and significantly decreased AIDS-related outcomes.¹⁰⁷ Subsequently, a second large, multinational trial demonstrated a further reduction in morbidity and mortality among HIV(+) individuals who had normal CD4 counts, > 500 cells/mm³, and received ART immediately versus delayed initiation when CD4 counts fell below 350 cells/mm³.^{108,109} Finally, The PARTNER study of more than 1000 mixed-status couples – one HIV(+), one HIV(–), 60% heterosexual, 40% homosexual – found no HIV transmissions with condomless sex when the viral load of the positive partner was very low, less than 200 copies/ml.¹¹⁰

This series of important studies has resulted in the current approach to use of ART – treatment as prevention (TasP): ART is now recommended as soon as HIV infection is confirmed, regardless of symptoms or timing, and for all AIDS patients, regardless of CD4 cell count or ongoing opportunistic infections.¹¹¹

Incredibly, analysis of long-term multinational cohort studies now shows that HIV(+) individuals who started therapy after 2008 and had only a minimally

depressed CD4+ count at the end of their first year on ART have a normal life expectancy.¹¹² There is still important work to be done because the survival benefits do not affect all HIV(+) individuals equally.¹¹³ Long-term survival with HIV infection is dependent on early diagnosis, linkage to and retention in care, and adherence to treatment, and these factors differ significantly by group. Specifically, there are important differences in survival by HIV transmission group, with lower life expectancies reported in all periods for individuals with a history of injection drug use. Possible reasons for these differences include increased comorbidity with greater non-AIDS-related mortality, as well as challenges with ART adherence, active drug use, hepatitis C co-infection, housing instability, and lower socioeconomic status. Differences in life expectancy by race are also evident, with white individuals having higher life expectancies in all periods. These differences may be reflective of underlying discrepancies in socioeconomic conditions causing limited/difficult access to care and problems with adherence, absent or limited health insurance coverage, fear of drug side effects, and/or stigma and fear of social disclosure. However, the gap in life expectancy between white and non-white individuals has decreased substantially, from 23 years in 2000–2002 to 8.5 years in 2006–2007.^{104–106} Disparities in observed life expectancy at age 20 narrowed for black versus white men who have sex with men (MSM) from 2004–2007 (33.0 vs. 52.3 years) to 2012–2015 (50.9 vs. 60.3 years).¹⁰⁵ Additional differences in life expectancies were noted by CD4 cell count at ART initiation – the lower the CD4 count even within the accepted range, the lower the life expectancy. Again, lower CD4 count at cART initiation can reflect delayed diagnosis and/or reduced access to care. These findings support the earliest possible initiation of antiretroviral therapy in all HIV-positive individuals.^{107–109,112} Even with recognized discrepancies in life expectancy, the results of early initiation of cART are truly amazing.^{112,113}

TasP has the potential to radically change the global outcome of HIV infection, significantly reducing population levels of HIV transmission. However, its effectiveness relies on universal HIV testing and, if positive, lifelong adherence to treatment because sustained viral suppression is the foundation for immune recovery, optimal health, and prevention of resistance and transmission. Monitoring with viral load and CD4 cell count is recommended with treatment change based on these results in countries where these tests are available. HIV testing is widely available in the United States and AIDS programs actively advocate for universal testing with regular periodic testing for high-risk groups. Drug resistance is still an important cause of treatment failure regardless of the clinical setting. As HIV multiplies in the body, the virus mutates and new strains that develop while an individual is taking antiretroviral medications can be drug-resistant. Drug-resistance testing is used to select an appropriate ART regimen. Careful medication adherence reduces the risk of drug resistance.

There have been other advances in preventing HIV infection in specific circumstances. Beginning in 2014, the CDC recommended prophylactic antiretroviral treatment (PrEP) for individuals who are HIV-negative but at high risk for HIV infection. Clinical trials in high-risk groups including gay and bisexual men,

sexually active heterosexual individuals with multiple partners, discordant couples with one partner HIV-positive where the infected partner refuses ART, and intravenous drug users, show that daily use of a two-drug combination pill containing tenofovir and emtricitabine (called Truvada) substantially decreases the risk of infection and the viral load in those who did become infected. For example, among gay and bisexual men with detectable drug levels (meaning they had taken the pill consistently), PrEP reduced the risk of infection by as much as 92%.^{114–116} In 2018, after a randomized trial showed similar positive results for PrEP in adolescents, the FDA approved Truvada for use in teenagers.

For people who need to prevent HIV after a single high-risk event of potential HIV exposure – such as unprotected sex, needle-sharing injection drug use, sexual assault or workplace accident – post-exposure prophylaxis, or PEP, is recommended.¹¹⁷ PEP should begin as soon as possible after exposure and must begin within 72 hours; treatment consists of a 28-day course of ART. If started within 72 hours after exposure and with 28-day adherence, PEP can reduce the risk of HIV infection by over 80%.

Evolving Epidemiology of HIV/AIDS in the United States: Implementation of Prevention and Treatment Advances

During the first 4 years of the epidemic, knowledge about AIDS increased dramatically as the epidemiology of the disease was described with identification of specific high-risk groups. As prevention and treatment regimens began to appear, the epidemiology of each high-risk group evolved independently, based on their unique demographics, the characteristics of the virus and the cluster of complex social and economic determinants of health.

Sexual Transmission: Gay and Bisexual Men

Young homosexual men were the first group identified with AIDS and to this day, MSM remain the group most frequently infected in North and South America, and in Western and Central Europe. In 2016, the CDC reported that gay and bisexual men accounted for 67% of all HIV diagnoses and 82% of diagnoses among males in the United States.¹¹⁸ MSM represent a much smaller proportion of new HIV diagnoses globally, but worldwide, this group continues to define a high-risk population.

As previously described, the first attempts at prevention arose from within the gay community in the United States with publication of information that condoms could be used as protection against becoming infected and spreading the epidemic. Multiple HIV seroconversion studies subsequently showed that latex condoms are 90–to 95% effective when used consistently.^{83–85}

The story of the intense involvement of the American gay population in the early years of the epidemic is effectively told in many settings but perhaps nowhere better than in Randy Shilts' book, *And the Band Played On*.^{87,119} The work of gay advocacy

groups and the involvement of committed celebrities were critical components in prevention efforts in the early years of the epidemic. However, until successful combination antiretroviral therapy (HAART/cART/ART) was validated in 1995, HIV infection and AIDS cases continued to increase every year with MSM remaining the largest group of individuals in both categories. The peak of new AIDS diagnoses in 1993 was associated with expansion of the CDC surveillance case definition: the AIDS surveillance case definition for adolescents and adults was expanded to include all HIV-infected individuals with severe immuno-suppression ($CD4+T$ lymphocytes $< 200/\mu l$ / $CD4+T$ lymphocyte percentage less than 14); or with pulmonary tuberculosis (TB), recurrent pneumonia or invasive cervical cancer.¹²⁰

Between 1995 and 2005, there were consistent declines in AIDS incidence and deaths in all groups including gay and bisexual males in response to the introduction of ART, as shown in Figure 6.3. From 1998 through 2000, AIDS incidence and deaths leveled off and AIDS prevalence continued to increase, with MSM again the largest group.¹²¹ By the end of 2000, the CDC reported there had been 774,467 people diagnosed with AIDS in the United States and 58% of these had died. There were more than 300,000 people living with AIDS, the highest ever reported, reflecting the large number being successfully treated with ART. Of these, 79% were men and 46% were infected through male-to-male sex, the most common mode of exposure.

In the early 1980s, most AIDS cases occurred among whites but cases among blacks increased steadily and by 1996, there were more cases among blacks than any other racial/ethnic group with increasing numbers of Hispanics and other minority groups as well. This trend continued and by the turn of the century, minority MSM emerged as the largest proportion of MSM with HIV/AIDS.¹²² Socioeconomic factors like isolation due to the stigma of homosexuality and homophobia in some minorities, poverty and unemployment, and lack of access to health care were associated with high rates of HIV risk behaviors among minority MSM and served as barriers to accessing HIV diagnosis and treatment.^{123,124} With ongoing improvements in treatment of HIV-positive individuals, AIDS deaths continued to decrease and the number of people living with AIDS continued to increase. In 2005, gay and bisexual men were still the most affected American group: of the estimated 322,125 male adults and adolescents living with AIDS in 2005, 59% had been exposed through male-to-male sexual contact, and 8% had been exposed through both male-to-male sexual contact plus injection drug use.¹²⁵

In theory, gay and bisexual men and their partners – both male and female – will be the groups to benefit most from initiation of combination ART as soon as HIV infection is confirmed.^{106–109} ART as prevention has the potential to radically change the course of the HIV/AIDS epidemic, but its effectiveness relies on universal HIV testing and lifelong adherence to treatment, a major challenge in the context of groups like young MSM and their partners who are among the most vulnerable to HIV infection. Innovative strategies are needed to increase the number of these at risk individuals using safe-sex methods and routinely testing for HIV infection.^{126,127}

There remain significant areas for improvement. From 2010 to 2014, the estimated number of new HIV infections in the overall American population declined by 10%. However, among gay and bisexual men who accounted for 82% of all new HIV diagnoses among males, racial differences persisted with an 11% decrease in white MSM, no change among African American MSM but an increase of 14% in Hispanic/Latino MSM. A study in 20 major US cities found that about 36% of black gay and bisexual men were infected with HIV, compared to 22% of MSM overall.¹²⁷ A more effective approach to HIV prevention, diagnosis and treatment in MSM and their partners from any background is needed.

HIV/AIDS in Women

After the first cases of heterosexually acquired AIDS were reported at the end of 1981 in young women with sexual partners who had AIDS or were at high risk for HIV infection, the number of females with AIDS steadily increased. The CDC added “female sexual partners of males with AIDS” as a risk category for AIDS in 1983, reflecting understanding that receptive vaginal sex was a high-risk setting for HIV infection. Of 88,510 cases of AIDS reported in adults in the United States from 1983 to 1988, the percentage attributed to heterosexual contact with HIV(+) individuals increased steadily from 13% in 1983 to 28% in 1988. By 1987, AIDS was the eighth leading cause of death in women aged 15–44 years, with reporting of HIV infection in women combining cases due to sex with HIV(+) partners and infection due to IV drug use. From the beginning, HIV infection in women disproportionately affected racial/ethnic minority groups: in 1988, the cumulative incidence of AIDS attributable to heterosexual contact per million population was over 11 times greater for blacks and Hispanics than for whites.¹²⁸

Over the next decade, AIDS cases in women continued to account for a significant proportion of all AIDS cases in the United States. By the end of 1990, reports to the CDC of AIDS cases among women exceeded 15,000, accounting for 11% of all reported cases in adults, an increase of 29% in women, compared with 18% in men. Among all cases of AIDS in women, 85% occurred among women of childbearing age. Approximately one fourth of these women were only 20–29 years of age at the time of diagnosis; many were probably infected as teenagers. By 1993, AIDS was the leading cause of death for African American women aged 25–44 years.¹²⁹

Despite significant advances in prevention of HIV infection, the HIV epidemic among women persisted largely unchanged until 2010, with 23% of new AIDS diagnoses occurring in women – almost 90% of these cases were attributed to heterosexual sex with 10% related to injection drug use. The number of annual HIV diagnoses in women finally declined from 2010 to 2017 with adult and adolescent women accounting for 19% of new HIV diagnoses. Nonetheless, more than 7000 women in the United States received a new diagnosis of HIV infection in 2017: 59% African American, 20% white, and 16% Hispanic/Latina.¹³⁰ This increased risk among racial/ethnic minorities reflects a multitude of unequal socioeconomic

burdens including poverty, violent crime, social disorder, incarceration rates, and male-to-female sex ratios among US black adults.^{131,132}

Women urgently need more options for HIV prevention: currently available forms are limited and many women are unable to negotiate condom use with male sexual partners. Pre- and post-exposure prophylaxis are highly effective methods, but problems with access, availability and daily pill compliance remain challenging. A vaginal ring which continuously releases the anti-HIV drug dapivirine is under investigation at this time. Designed to be a discreet, long-acting HIV prevention option for women, the wearer replaces the product herself every four weeks.¹³³ Additional options for safe and effective prevention of HIV infection for women are under investigation.

Injection Drug Use

In December 1981, just 6 months after the first AIDS reports in gay men, AIDS cases were reported for the first time in men and women who were intravenous drug users (IDUs).⁴ By the end of 1985, 17% of all AIDS cases in the United States occurred in IDUs.¹³⁴ In this group, identified risk factors for HIV infection were shared syringes and other injection equipment, especially in communal settings like “shooting galleries”; the number of drug injections/ month; and high-risk sexual behavior under the influence of drugs or in exchange for drugs. For women, the number of heterosexual partners who used drugs was also significantly associated with HIV infection.¹³⁵

Prevention efforts have focused on these risk factors and from the beginning, prevention programs in IDUs have been community-based, using mobile vans, storefronts and street corners to directly reach known at-risk populations and connect them to prevention programs, HIV testing, and care and treatment services. Needle and syringe programs that provide or exchange sterile equipment have been consistently shown to be highly effective at reducing new HIV infections, often also providing counseling, safer-sex education, HIV testing and referrals to drug treatment programs. The first comprehensive needle exchange programs were established in North America in 1988. Despite their proven success, there has never been consistent federal funding for needle/syringe supply programs so their distribution is inconsistent, based on state funding and community support.¹³⁶ Medication-assisted addiction treatment programs where drugs like methadone are substituted for opioids are effective treatment for drug dependence, eliminating risk behaviors associated with injection drug use and preventing HIV transmission. IDUs who do not enter addiction treatment programs are up to 6 times more likely to become infected with HIV. Again, funding is a critical deterrent to access to treatment for drug dependence.¹³⁷ HIV infection in IDUs is an ongoing problem: with the recent dramatic increase in opioid abuse in the United States, there have been community outbreaks of HIV infection related to injection of these drugs.¹³⁸

But overall, the combination of education and intervention has significantly decreased the proportion of new HIV infections in IDUs in the United States. From

2010 to 2014, among people who inject drugs, annual HIV infections declined by 32%. In 2015, only 6% of new HIV infections were among people who inject drugs; another 3% combined homosexual behavior with drug injection.¹³⁹

Transfusion of HIV-Contaminated Blood and Blood Products

Individuals with hemophilia who became infected with HIV were critical in understanding the pattern of infection, providing the first suggestion that the then-theoretical agent that caused AIDS might be transmissible in blood products.¹² Testing of frozen stored plasma in a single-center series revealed that the first HIV infections in this group occurred as early as 1978.¹⁴⁰ Prospective follow-up of a cohort of 310 hemophiliacs with HIV seroconversion definitively confirmed the long incubation period between infection and the appearance of AIDS. The incidence rate of AIDS after HIV infection was found to be directly related to age, ranging from an average 8-year cumulative rate of 13% for individuals less than 17 years to 44% for those over 35.¹⁴⁰ Because of widespread prior contamination of blood factor concentrate, the HIV infection rate in the early years of the AIDS epidemic was higher among hemophiliacs than among any other group. From the late 1970s to the mid-1980s, about half of all people with hemophilia became infected with HIV after receiving contaminated blood products – among those with severe hemophilia who required repeated clotting factor infusions, an estimated 90% were infected with HIV. Ultimately, ~6000 American hemophiliacs and at least 8000 globally were infected with HIV by receiving contaminated clotting factor transfusions.

Despite suggestive guidance from the CDC, the plasma fractionation industry failed to initiate any approach to identifying infected blood donations so new infections continued until 1985.¹⁴¹ After the HIV screening test was validated in 1985, universal screening of the blood supply dramatically reduced the risk of HIV transmission through clotting factor transfusions. Since 1987, specific inactivation methods have been used to effectively eliminate all viral contaminants in clotting factor products with no further transmissions of HIV through clotting factor products in the United States.

The history of HIV infection following transfusion with contaminated blood parallels the story in hemophiliacs. The first case was recognized in December 1982 when a 20-month-old baby was diagnosed with AIDS; as a newborn, he had received a platelet transfusion from a homosexual who was well when he donated blood but who subsequently died of AIDS.^{18,19} Within months, there were multiple reports of transfusion-associated AIDS cases, many with confirmation that transfused blood components were from donors with AIDS.^{142,143} At this early stage in the epidemic, it was these reports combined with the evidence from hemophiliacs that confirmed that the AIDS agent was blood-borne and could be transmitted by transfusion of blood and blood products.

The CDC initiated official meetings with the blood services community to address this issue, but despite these efforts and mounting concern on the part of many scientists and physicians, the blood donor industry was skeptical, reportedly

because the number of AIDS cases was small compared to the enormous number of transfusions received, and concern that the volunteer donor supply would be interrupted if any screening procedures were put in place.¹⁴¹ The CDC's 1983 official recommendations for the prevention of AIDS did include a specific recommendation that members of "high-risk" groups should not donate blood, but no surrogate screening procedures or direct questioning of donors about potential risk categories was recommended.⁸⁵ Spurred by news reports of AIDS from transfusions, blood donation before a planned procedure to be used for autologous transfusion and directed donations from family members became very popular during this time period. Mathematical projections estimate that approximately 12,000 people in the United States acquired a transfusion-associated HIV infection between 1978 and 1984.^{143,144} When the ELISA test for identification of HIV infection was adopted as the universal standard for screening donated blood in 1985, there was an immediate, precipitous decline in transfusion-associated HIV infection.⁷⁷ By 1995, less than one in half a million screened blood donations were estimated to be contaminated with HIV.¹⁴⁵

Since then, the risk for transfusion-transmitted HIV infection has been almost eliminated by using questionnaires to exclude donors at elevated risk for HIV infection combined with highly sensitive laboratory screening tests to identify and exclude infected blood donations. The risk of acquiring HIV infection through blood transfusion today is estimated conservatively to be one in 1.5 million, based on 2007–2008 data. Very rarely, an individual donates blood during the window period after HIV infection and the donated blood tests positive. The last time this was reported in the United States was 2008.¹⁴⁶

Maternal–Infant Transmission of HIV: Babies with HIV/AIDS

In 1982, the CDC first reported cases of AIDS in infants and young children whose mothers had or were being investigated for AIDS included six young children who died with opportunistic infections and unusual cellular immuno-deficiencies similar to those seen in adults with AIDS. The reports suggested the horrible possibility of transmission of the still unknown AIDS agent from mother to child, *in utero* or shortly after birth.²⁰

The 1985 development of antibody testing allowed a better picture of the natural history of perinatally acquired HIV infection. In this time period in the United States, the incidence of HIV/AIDS in women was increasing exponentially with two major sources of infection: injected drug use and sex with partners infected with HIV. Eventually, it became clear that 15–40% of infants born to HIV-infected mothers become infected *in utero*, during labor and delivery and/or by breast-feeding.¹⁴⁷ Mothers with AIDS with high viral counts and/or with low CD4+ counts were found to have significantly higher rates of HIV infection in their babies.¹⁴⁸

The natural history of vertically acquired HIV infection in children is extraordinarily variable with a wide spectrum of age at symptom onset and clinical

manifestations. In 15–20% of infected infants, severe immunodeficiency develops in the first year of life with failure to thrive and recurrent serious infections and/or encephalopathy; these early symptoms predict a shorter survival. In a small subset – often children who are infected after birth by breast-feeding – the children can be completely well for several years before unusual and recurrent infections develop, reflecting immune compromise. Overall, without antiviral treatment, median survival ranges from 75 to 90 months with only 70% of children surviving to 6 years of age.¹⁴⁹

In the early days, diagnosing HIV infection in infants and children was challenging, because antibodies cross the placenta. Testing newborns was not an effective way to identify infected newborns so even after antibody testing became available, the only recommendation was that pregnant women in high-risk groups be offered counseling and voluntary HIV testing.¹⁵⁰ Using this voluntary system, the majority of HIV(+) pregnant women were not identified and the number of children with perinatally acquired HIV infection increased dramatically. In 1993, the CDC estimated that 14,920 HIV-infected infants had been born in the United States, with two-thirds of this number in the preceding 5 years; 84% of these cases were African American or Hispanic infants.¹⁵¹

With no effective treatment, management was limited to prophylactic gamma globulin injections and broad-spectrum antibiotic prophylaxis. Over time, PCP – the same rare presentation seen in the original AIDS cases in young homosexual males – proved to be the most common opportunistic infection in American children with AIDS and in 1991, the first guidelines for PCP prophylaxis were published, based on age-associated CD4+ cell counts.¹⁵² The guidelines had little impact on the dismal prognosis for these young children so they were revised, recommending specific PCP prophylaxis beginning at 4–6 weeks of age in all HIV-infected infants. At this time, AIDS was the seventh leading cause of death among children 1–4 years of age.¹⁵³

A major breakthrough occurred in 1994 when a three-part zidovudine (AZT) regimen given during pregnancy and labor to HIV-infected mothers and to their newborn infants reduced HIV transmission by almost 70%.¹⁵⁴ This was immediately recommended by the CDC and the US Public Health Service along with a repeat recommendation for voluntary HIV testing of all women during pregnancy.¹⁵⁵ There was a steep and sustained decline in new HIV/AIDS cases in infants and children in the United States from this point forward. Between 1992 and 1996, the number of mother-to-infant HIV transmissions in the US dropped by two-thirds, primarily as a result of treatment of HIV-infected mothers and their newborns with AZT. From 1985 to 1999, AIDS cases among children declined by 81%, but with women accounting for 23% of AIDS cases in the US (compared with 7% in 1985) and one-third of new HIV infections occurring among women, the problem of perinatal infection remained an ongoing challenge.¹⁵⁶ Subsequent studies showed that when HIV(+) mothers received combination antiretroviral treatment (cART) reducing the maternal viral load to undetectable levels – the

recommended treatment for all HIV(+) adults – *and* did not breastfeed, the rate of perinatal HIV transmission was reduced to less than 2%.^{157,158}

Optimal implementation of this highly effective regimen requires universal HIV testing early in pregnancy and guidelines for testing lagged behind available treatment for years. Universal HIV testing is now recommended in all pregnancies and prenatal testing has increased dramatically. However, testing is still not mandatory, so there are still women who present in labor without any HIV evaluation. In this situation, rapid HIV testing is recommended so that ART can be emergently implemented. The combination of prenatal HIV testing, combination ART and avoidance of breastfeeding has dramatically decreased the incidence of new, perinatally acquired HIV cases in the United States every year since 1995. In 2015, the CDC reported there were only 120 cases of perinatal HIV infection, half the number reported in 2010.¹⁵⁹

HIV Infection/AIDS in the USA: Current Statistics (2016–2019)

- By the end of 2017, the cumulative number of individuals in the United States ever diagnosed with AIDS was 1,281,787.¹⁶⁰
- At the end of 2016, an estimated 1.1 million people aged 13 and older were living with HIV infection in the United States, including an estimated 14% who were unaware of their diagnosis.¹⁶⁰
- Annual new HIV infections in the United States have decreased by more than two-thirds since the height of the epidemic in the mid-1980s, when there were more than 150,000 new infections every year. Between 2008 and 2017, the number of annual HIV infections in the United States fell by 18%— from an estimated 45,700 to 38,700 – according to the most recent CDC estimates available.¹⁶¹
- Gay and bisexual men (MSM) remain the subpopulation most affected by HIV in the United States, accounting for 67% of new HIV diagnoses. Among all MSM who received an HIV diagnosis in 2016, African Americans accounted for the highest proportion (38%), followed by Hispanics/Latinos (29%) and whites (28%).
- After MSM, sexually acquired HIV infections in heterosexuals are the next highest group, accounting for 24% of new HIV diagnoses in 2017. Heterosexual men accounted for 7% of new HIV diagnoses and heterosexual women for 16%. From 2012 to 2016, HIV diagnoses among heterosexuals declined by 8–9%.
- An estimated 258,000 women had HIV infection in 2016, representing 23% of all people with HIV: 86% were attributed to heterosexual sex and 14% to injection drug use. Of all female HIV(+) cases, an estimated 89% were aware of their infection.
- Injection drug users accounted for 6% of new HIV diagnoses in 2017. Among people who inject drugs, HIV diagnoses decreased by 17% from 2012 to 2016.

- Teens and young adults continue to be at risk, with those under 35 accounting for 56% of new HIV diagnoses in 2017. Among young people, gay and bisexual men and minorities have been particularly affected.
- Perinatal HIV transmission, from an HIV-infected mother to her baby, has declined dramatically in the US, largely due to increased testing efforts among pregnant women, and ART, which prevents mother-to-child transmission. In 2015, the CDC reported only 120 cases of perinatal HIV infection, half the number reported in 2010.¹⁵⁹
- Among HIV-positive individuals reportedly receiving continuous anti-HIV treatment, only 51% are virally suppressed.¹⁶¹
- In 2015, there were 6531 deaths with diagnosed HIV in the United States. This is down from the peak of almost 42,000 deaths which occurred in 1995.
- More than 700,000 people have died with AIDS in the United States since the beginning of the epidemic.¹⁶²

Global HIV/AIDS

History of Global Spread

It may have seemed like an American disease when the first case reports appeared in the summer of 1981, but by early in 1982, the first recognized AIDS case from outside the United States was reported in France.¹⁶³ Early in the epidemic, European doctors recognized and reported episodes of illness corresponding to the description of AIDS which had occurred before 1979 in Europeans and Africans.^{164–167} By June 30, 1983, the WHO was aware of 153 European AIDS cases, predominantly from Belgium, France, West Germany, Switzerland, Britain and Denmark. The same risk groups as in American cases were identified in the majority of patients, but a subset were Africans from sub-Saharan Africa and visitors to that area who had subsequently relocated to Europe.¹⁶⁸ The disease reports of the Africa-related cases matched the AIDS definition from the CDC, but the epidemiologic profile did not match the profile defined by US cases – instead, cases occurred equally in men and women and there was no history of homosexuality, drug addiction or blood transfusions.^{169,170} By November 1983, 22% of all European AIDS cases were among people originally from sub-Saharan Africa.¹⁷¹ Based on personal experience, Chumuck et al. wrote: “We believe that AIDS is a new disease that is spreading in Central Africa.”¹⁷²

The African AIDS cases led Belgian researchers to begin investigating in Zaire, the country of origin for many of these patients. Zaire was previously known as the Belgian Congo and Belgium still had strong connections with this part of Africa. In 1983, the US Agency for International Development (USAID) funded a limited investigation by American and Belgian investigators in Kinshasa, the capital of Zaire. Working with local physicians, the team identified 38 cases of AIDS in the main hospitals of Kinshasa, most already very ill. As with the small number of cases of African heritage seen in Europe, half the patients were women. On average,

they had been symptomatic for 10 months with severe progressive weight loss during that time. There was no history of intravenous drug use or homosexuality in any case, but as a group, the patients had multiple sex partners in the year before the illness began. Astonishingly, 26% of the patients died during the 3 weeks the research team was in Kinshasa.^{173,174}

In this same time period, doctors in Uganda were confronted by a surge in cases of a severe wasting disease – known locally as “slim disease” – accompanied by a dramatic increase in opportunistic infections, especially tuberculosis. Females and males were equally affected and most patients were heterosexuals who had a history of multiple sex partners. The doctors who described these patients recognized the similarity to the cases of AIDS seen in neighboring Zaire, and subsequent testing confirmed that 80% of these cases were HIV-positive.¹⁷⁵

After the initial clinical recognition of the link between “slim disease” and AIDS, research was initiated to discover transmission patterns, risk factors, and the prevalence of HIV in Uganda. By 1990, HIV prevalence in pregnant women in Uganda’s capital had peaked at over 30%. At around this time, the cases reported from Zaire and Uganda were recognized as just the very tip of the HIV/AIDS infection pyramid in Africa.

Origin of HIV

In reading about this time period, it is clear that after seeing their first patients with AIDS, physicians in Europe, Africa and the United States began to recall unusual, undiagnosed patients they had taken care of in the past whose case profiles resembled the devastated immune status seen with AIDS. When the first test for HIV became available in 1985, blood and tissue samples from some of these patients were tested and identified as HIV-positive. In the United States, the earliest identified case was a 15-year-old boy who presented with disseminated chlamydial infection in 1968 and died of pneumonia in 1969; at autopsy he was found to have disseminated Kaposi’s sarcoma and antibody testing for HIV was positive.¹⁷⁶ A Norwegian sailor with a history of visiting ports in Africa in the early 1960s developed the picture of clinical AIDS in 1966, followed by his wife and child. Subsequently, serum testing was positive for HIV in all three.¹⁷⁷ Recovery of HIV-1 sequences from a paraffin-preserved lymph node sample of a female from Kinshasa confirmed the presence of HIV infection there in 1960. Viral sequencing of a plasma sample from an African male from Kinshasa obtained in 1959, definitively confirmed the presence of HIV-1 and authenticated this case as the oldest proven human HIV-1 infection.¹⁷⁸

Inevitably, identification of these cases led to investigation of the origin of the human immunodeficiency virus with a focus on central, sub-Saharan Africa where the earliest known cases were identified. As early as the mid-1980s, a monkey or simian virus that very closely resembled HIV-2 was discovered to cause immunodeficiency in captive macaques. Subsequently, this simian immunodeficiency virus (SIV) was found in multiple primates in sub-Saharan Africa with the prevalence of naturally occurring infection ranging widely; in most species, the virus appeared to cause

no detectable illness. Ultimately, phylogenetic studies show that SIV_{smm} – for “SIV sooty mangabey” – was confirmed as the monkey ancestor for HIV-2 with transfer to humans by skin or mucous membrane contact with blood, presumably related to bushmeat hunting. A simian virus that closely resembled HIV-1 was discovered in chimpanzees in 1990 in south-east Cameroon. Using non-invasive analysis of urine and fecal samples, scientists discovered that in monkeys, SIV_{cpz} (SIV chimpanzee) is spread primarily through sexual routes with animal migration carrying the infection from one community to another. Combined behavioral and virologic studies show that SIV_{cpz} infection is associated with an AIDS-like illness in chimpanzee colonies. As with SIV_{smm} , spread of SIV_{cpz} to humans is thought to have occurred via incidents related to hunting and slaughtering of chimpanzees as bushmeat.

Molecular phylogenetic studies like the ones we first encountered relative to the influenza virus can be used to analyze the genetic sequences of a cluster of similar viruses. The greater the similarity between the genetic sequences of two viruses, the greater the likelihood that they share a recent common ancestor; based on analyses like these, a family tree that shows the pattern of evolution of a virus can be created. From phylogenetic studies, the ancestral simian viruses to SIV_{cpz} and SIV_{smm} are thought to have evolved from primate lentiviruses that emerged in Africa some time after the divergence between African and Asian Old World monkeys, within the last 10 million years.¹⁷⁹ Applying these same techniques to viruses from humans, a common ancestor of HIV-1, group M, the pandemic form of the virus, has been shown to have emerged in Kinshasa, the Democratic Republic of the Congo (DRC) – once Leopoldville, the Belgian Congo – in the 1920s.¹⁸⁰ Genetic sequencing of the two earliest tissue samples from Kinshasa in 1959 and 1960 showed significant diversity indicating that by 1960, HIV had evolved enough that there were two distinct subtypes in circulation. Based on this known rate of HIV mutation, phylogenetic analysis indicates the virus emerged as early as the turn of the century.¹⁸¹ The viruses infecting monkeys and apes are thought to have crossed over into humans sporadically for a long time, most likely when humans were scratched or cut while hunting and butchering monkeys and chimps. That enabled the virus to adapt to humans. Those ancient infections never spread because human population density was so low in the jungle at that time. It was only when the virus traveled to Kinshasa at a time of explosive population growth that the HIV/AIDS epidemic started.

The cross-species transmission of SIV to humans likely occurred in Cameroon where the chimpanzees with SIV_{cpz} most closely resembling HIV group M were identified and the virus then travelled to Kinshasa in jungle hunters via the river system that linked the two countries for rubber and ivory transport. It is speculated that HIV was brought to the city by an infected individual who travelled from Cameroon by river down into the DRC. This theory is wonderfully expounded by David Quammen in his book, *The Chimp and the River: How AIDS Emerged from an African Forest*.¹⁸² On arrival in Kinshasa, the virus entered a wide urban sexual network and spread quickly. Using the earliest archival HIV-1 sample from 1959 and molecular genetic analysis, researchers have created a phylogeographic

model demonstrating that HIV-1 spread from Kinshasa throughout the DRC and the Congo River basin as the population migrated over the next 30–40 years.¹⁸¹ Historical transportation data from this period suggest that travel on railways and waterways is compatible with this migration path and, therefore, transport of HIV-1 from Kinshasa to the other major population centers of the region. Based on this analysis, HIV group M had spread to all the major cities of the DRC by 1970. The development of the AIDS epidemic in Africa reflects the period of “massive demographic growth, urbanization and associated social change” that occurred in the region at that time.¹⁸³

By linking phylogenetic tree shape to the demographic history of sampled populations, group M was shown to have undergone slow exponential growth between 1920 and 1960 followed by much faster exponential growth – almost 3 times faster – after 1960. This coincides with public health data that suggest that transmission rates of group M increased dramatically in this time period, as commerce and the sex trade expanded along with increased travel. Analysis of group M subtypes shows that the lineage ancestor of subtype B originated in Kinshasa in ~1944 before it was carried to North America. HIV-1 group M subtype B is the original virus identified by Montagnier and Gallo in 1982. Subtype B remains the dominant subtype in the United States from which it spread to become the most widely dispersed global pattern. The same analytic techniques show that subtype C was carried from southern DRC mining regions to southern Africa, where it is now the dominant group M subtype.¹⁸⁴

The question of Haiti’s involvement in the early AIDS epidemic in North America was also addressed by combining phylogenetic, molecular evolutionary, historical, and epidemiologic data. Based on early reports of a high prevalence of AIDS in Haitian immigrants to the United States, there had always been speculation that the unknown agent that caused the epidemic originated in Haiti.¹² By sequencing HIV-1 samples from the earliest known AIDS patients from Africa and those early Haitian AIDS patients, researchers showed that HIV-1, group M, subtype B moved from Africa to Haiti in ~1966, a time when Haitian professionals who had worked in what was the Belgian Congo in the 1960s returned home. Phylogenetic analysis and molecular clock techniques indicate that subtype B spread from there to the United States and Canada after a single chance migration of the virus out of Haiti in ~1969.¹⁸⁴ This is compatible with the average HIV incubation period of 10 years, with the first American infections occurring in 1969 and the first clinical cases of AIDS appearing in the late 1970s.

The Pattern of Global Spread

With understanding of the origin and early spread of HIV-1, the development of the global epidemic of HIV/AIDS is more easily appreciated. After the first cases in Europe were infected by contact with HIV carriers from North America, spread was rapid – by the end of 1985, AIDS had been reported in 51 countries and on every continent except Antarctica.

Analysis of a large data set of globally representative HIV-1 group M subtype B strains using phylogeographic and statistical techniques mapped the global migration of this original virus subtype from the United States over the last 40 years.^{185,186} Analysis of viral sequences from multiple countries revealed that the American continent and the Caribbean acted as the predominant source for outward spread of the epidemic. As documented by the original cases of AIDS, Western Europe was a region where subtype B infections were introduced early from North America and multiple other geographic areas and spread mainly among regional populations. Early spread to Central and Eastern Europe was minimal and delayed until the end of the Cold War, when travel between Western and Eastern European countries increased dramatically, accompanied by the arrival of HIV-1. In summary, HIV spread around the globe after the mid-1960s reflected both the pattern and volume of human mobility over this time period, with the predominant migration from North America to Western Europe and then beyond.^{185,186}

As the epidemic evolved around the world, the disease pattern reflected the demographics and sexual/social customs as well as multiple structural, societal determinants of health like poverty, healthcare access, socioeconomic status, education, and homophobia in the involved regions. In Africa, after the original clinical cases in the 1970s, HIV/AIDS spread quietly but inexorably in heterosexual relationships from Eastern and Central Africa to Southern Africa through the 1980s until the early 1990s, when there was a period of rapid exponential growth resulting in this area becoming the largest HIV/AIDS site in the world.^{187,188} By 1995, the WHO estimated that of 20.1 million adults with HIV/AIDS worldwide, 12.9 million cases were in sub-Saharan Africa. Throughout Africa, tuberculosis was (and is) the infection that took greatest advantage of the compromised immune system in people with AIDS, not the rare opportunistic infections seen in North America and elsewhere in the developed world. Tuberculosis remains the leading cause of death among African people living with AIDS. In 2012, people living with AIDS accounted for 1.1 million (13%) of the estimated 8.7 million people who developed tuberculosis globally.

In industrialized countries like the United Kingdom and Western Europe, HIV appeared in the early 1980s among homosexual men and IV drug users and then spread to the heterosexual population.^{185–188} Beginning in the late 1980s, the epidemic grew rapidly in South-East Asia, where spread was predominantly in commercial sex workers and intravenous drug users. The epidemic is known to have been well-established in urban centers in India by the early 1990s, although actual surveillance data are limited. In Japan, the largest proportion of early reported AIDS cases was in hemophiliacs who received HIV-infected blood products in the early to mid-1980s. Finally, in Eastern Europe and Central Asia, the pattern and magnitude of early HIV infection was not defined until after 1987 when the Soviet Union began to officially report HIV infections. After the fall of the Soviet Union in 1991, heroin and other injectable drugs became easily accessible to Russians. From the late 1990s onward, as trafficking routes into Russia further developed, HIV infection rates across the region began to rise steadily to currently 10–15%

each year – a pace comparable to the infection rate in the United States in the early 1980s. There are currently at least 1.5 million people in Russia from a population of 140 million who have been diagnosed with HIV/AIDS. In 2014, the most recent year for which data are available, the Russian Federal AIDS Center reported that intravenous drug use accounted for 58% of HIV infections with the rest from sexual transmission.¹⁸⁹

The Evolving Global Epidemiology of HIV Infection and AIDS: Implementation of Prevention and Treatment Advances

The first official responses to the global epidemic emerged in 1988, when the World Health Organization (WHO) launched the Special Program on AIDS, later called the Global Program on AIDS or GPA. Led by Jonathan Mann, the program demanded a human rights-based response to the pandemic. Over the next decade, the GPA became the largest program in the history of the WHO, providing a basic international framework for HIV prevention. The GPA strongly supported individual behavior change in high-risk groups like homosexuals, with sex education in schools and explicit condom promotion and provision. Safe-sex interventions directed at heterosexual populations were also extended to gay and bisexual men. By the early 1990s, with GPA leadership almost all developing countries had established their own, national HIV prevention programs with varying degrees of success reflecting the difficult political issues associated with a sexually transmitted disease in a wide variety of cultures.¹⁹⁰

When successful antiretroviral therapy appeared in 1995, global spread of the infection was still increasing: peak incidence of new HIV infections globally was in 1998 and by the end of 2002, AIDS was the leading cause of death worldwide among people aged 15–59.¹⁹¹ By 2004, 15 million children worldwide had lost one or both parents to HIV/AIDS and AIDS-related deaths were still on the rise, peaking in 2005. In 1996, in response to the growing global epidemic, the United Nations established UNAIDS, the Joint United Nations Program on HIV/AIDS, to address the critical international need to focus aid and resources on treatment: for example, in 2000, there were more than 20 million people living with AIDS in sub-Saharan Africa, but only 8000 were accessing drug treatment.

The 13th International AIDS Conference in 2000 marked a critical turning point, with UNAIDS raising global public consciousness about the spiraling AIDS mortality in Africa and the impossibly high cost of antiretroviral drugs. Under international pressure led by UNAIDS, generic producers made ART drugs available at much lower costs and pharmaceutical companies dropped their prices on brand-name products. This was followed by the Doha Declaration that certified that states could circumvent patent rights to access medicines deemed essential for public health.¹⁹¹ In 2001, the Global Fund to Fight AIDS, Tuberculosis and Malaria was created under UN direction to fund country-owned initiatives against these diseases – since its creation, 60% of funds have gone to fund HIV/AIDS programs. In 2003, US President George Bush announced the President's Emergency Plan

For AIDS Relief (PEPFAR); working in over 60 countries, PEPFAR has made major contributions to the global HIV/AIDS response, providing ART to millions of people. With these international funding sources, there has been dramatic progress with major gains in global initiation of antiretroviral therapy. By the end of 2005, a report released by the World Health Organization and UNAIDS showed that the number of people on HIV antiretroviral treatment in developing countries had more than tripled since 2003 to 1.3 million.¹⁹² Prevention and treatment efforts in different HIV transmission groups over the last 14 years have varied from country to country reflecting resources and the regional sociopolitical climate. As an example, global HIV infections caused by contaminated transfusions of blood and blood products varied widely between countries. After development of a specific test for HIV in 1985, screening of the blood supply dramatically reduced the risk of HIV transmission through blood, blood product and clotting factor transfusions. Use of specific inactivation methods ultimately eliminated all viral contaminants in clotting factor products, although the time for this to be accomplished varied widely between countries. Thousands of individuals were infected by transfusion of contaminated blood products with scandals involving government officials and the commercial blood supply widely reported in the United Kingdom and Japan.

Sexual Transmission of HIV

Gay and Bisexual Men (MSM); Female Partners of HIV(+) Men

While HIV infection in gay and bisexual men has never been a major transmission group in Africa or any other developing country, it remains a high-risk group in highly developed societies, especially in Western Europe, Latin America and South America. Globally, gay men and other men who have sex with men are 19 times more likely to be living with HIV than the general population.¹⁹²

Global prevention efforts have included homosexuals but specific prevention and treatment campaigns directed at MSM are seen much more commonly in areas where this pattern of transmission predominates. In 2007, the American Foundation for AIDS Research launched the MSM Initiative, a global program to support HIV prevention, treatment, and advocacy efforts for men who have sex with men. Early initiation of ART in HIV(+) individuals and effective use of pre- and post-exposure prophylaxis have the potential to radically change the global course of HIV infection and HIV transmission in this high-risk population.^{107–117} However, this requires universal HIV testing and sustained adherence to treatment, a major challenge in the context of groups like young MSM who are among the most vulnerable to HIV infection. As in the United States, strategies to increase the number of gay and bisexual men testing for HIV and committing to treatment adherence are critically important.

Heterosexual transmission of HIV infection has always been much more important globally than in the United States, especially in sub-Saharan Africa. In 2017, HIV was the leading cause of death worldwide among women of reproductive age, and half of adults living with HIV worldwide were women.¹⁹² HIV/AIDS

represents a major public health crisis for women, especially young women¹⁹³: in South Africa, for example, there are estimated to be 2300 incident HIV infections per week in adolescent girls, and girls in this age group are twice as likely as men to contract HIV. The global health impact of HIV/AIDS is particularly important in vulnerable female populations like adolescents and children, commercial sex workers, women who have suffered trauma, abuse, violence, substance abuse and serious mental illness, and women who have been trafficked for labor or sex work. HIV/AIDS is a critical factor in the global health of women. Women urgently need more options for HIV prevention – in 2017 alone, nearly 870,000 women and girls acquired HIV, according to UNAIDS.¹⁹² Currently available forms of HIV prevention for women are limited, and many women are unable to negotiate condom use with male sexual partners. Pre- and post-exposure prophylaxis are highly effective, but problems with access, availability and daily pill compliance remain challenging. Additional long-acting methods to prevent HIV infection in women are urgently needed.

Injection Drug Users (IDU)

Injection drug use has become a major and increasing cause of global HIV infection extending east across Europe into Eastern Europe, Central Asia and the Far East. As of 2015, nearly 30% of global HIV infections were due to unsafe injection drug use. Implementation of effective treatment programs has varied widely between countries. For example, early in the global epidemic, Amsterdam had one of the world's highest rates of injection drug use – and one of the worst drug-associated HIV epidemics. In 1984, Amsterdam set up one of the first needle and syringe programs as concerns about the growing epidemic of HIV increased. This long-established needle exchange program is reported to have virtually eliminated IDU-transmitted HIV transmission there.¹⁹⁴ Rapid localized spread of HIV among IDUs was reported from multiple geographic centers extending from Western Europe to the far East in the 1980s and 1990s. In most of these areas, the steep increasing incidence leveled off as specific intervention policies for IDUs and safe-sex education practices were implemented. By contrast, the rate of HIV infection in Russia is still rising rapidly, with intravenous drug use accounting for at least 58% of HIV infections. The Kremlin has refused to adopt the globally accepted, evidence-based strategy of drug substitution therapy that has significantly reduced the spread of the epidemic among drug users in other countries. Access to needle exchange programs in Russia is also very limited. Instead, the Russian government focuses on the criminalization of drug use and the stigmatization of key populations at risk.¹⁸⁹ In summary, IDU remains an important cause of global HIV infection, with the introduction of education, treatment and prevention programs varying widely between countries.

Global Perinatal Infection

The global picture of perinatal HIV infection is best exemplified in sub-Saharan Africa, the epicenter of the global pandemic which has accounted for 65–70% of

all new HIV infections since the first cases appeared there. From the outset, more than half of these new infections have been in women with a corresponding very high rate of perinatal transmission. Through the mid-1980s, accurate estimates of maternal and perinatal involvement were unavailable, but by 1989, the WHO Global Program on AIDS reported there were 2.5 million women and half a million children infected with HIV-1 in sub-Saharan Africa alone.¹⁹⁵ With no virus-specific treatment, the number of infected women and infants skyrocketed. In 1991, perinatal AIDS was estimated to have increased global infant and child mortality by 30%.¹⁹⁶ By 1997, UNAIDS reported that the number of children less than 15 years of age infected with HIV since the start of the epidemic in the late 1970s had reached 3.8 million – 2.7 million of these children had already died.¹⁹⁷

In 1994, the discovery that AZT treatment of the mother and baby at the time of delivery effectively blocked HIV infection in 70% of cases was a tremendous advance, but one that was initially largely unavailable outside of industrialized countries.¹⁵⁴ Controversy arose about the ethics of prophylactic research trials to prevent maternal–fetal transmission of HIV in the less-developed world, centered around the need for placebo-controlled trials, the virtual impossibility of true informed consent, failure to provide an intervention of known efficacy and potential subject exploitation.^{198–201} While this discussion was still ongoing, the CDC reported that a short course of oral AZT given late in pregnancy and during delivery with no infant dose had been proven effective in reducing perinatal HIV transmission in a placebo-controlled study in Thailand.²⁰² Confirmation that sound evidence had shown there was an available, effective and relatively easy to implement intervention appeared to resolve the ethical controversy. Ultimately, subsequent studies showed that when HIV(+) mothers received combination ART and avoided breastfeeding, the rate of perinatal HIV transmission was reduced to less than 2%.¹⁵⁷ Breastfeeding was addressed by considering the balance of factors – in a developing country, breastfeeding was almost always the better choice for nutrition and safety reasons and often the only choice because of economic and practical constraints.

Initially, efforts to extend the use of ART to resource-poor settings like sub-Saharan Africa were limited.²⁰³ In 2000, with the major breakthrough in international access to ART, UNAIDS negotiated an Accelerating Access Initiative which was followed in 2001 by a United Nations Special Session Declaration that ART was essential to the fight on HIV/AIDS. The WHO followed by adding antiviral medications to their Essential Medicines List and developing a public health approach to treating individuals in resource-poor settings.¹⁹¹ Over the next 15 years, multiple strategies were attempted in the effort to diagnose maternal HIV infection and prevent infant transmission by delivering antiretroviral therapy in resource-limited settings all over the world.^{203–206} All these studies underscored the importance of offering ART interventions to pregnant women with HIV infection whenever and wherever they were identified – during pregnancy, during labor and delivery, or as an intervention with the newborn baby. Over the next decade,

there was a progressive increase in ART use for prevention of HIV transmission from mother to child using a variety of protocols. Each program was theoretically efficacious for preventing transmission but implementation was fraught with problems because of the variability and complexity of the recommendations – and most importantly, because many iterations left HIV(+) women without treatment after delivery.

The WHO followed the emerging evidence with serial recommendations for the prevention of peripartum mother-to-child transmission in developing countries with the first published guidelines on the use of ART for HIV infection among adults and adolescents in 2002, and on the use of ART to prevent mother-to-child HIV transmission in 2004.²⁰⁷ The 2006 update of the guidelines introduced the concept of a public health approach, with simplified and harmonized ART regimens.²⁰⁸ Then, in 2013, for the first time, WHO revised and combined all ART-related documents into consolidated guidelines recommending ART drugs for HIV treatment and prevention across all age groups and populations including pregnant women. These guidelines were updated in 2016 with augmented global guidance to reflect the strong science base supporting the benefit of early and sustained HIV treatment.²⁰⁹ The 2016 WHO guidelines now call for “test and treat” strategies – initiating all people diagnosed with HIV infection on ART as soon as possible after diagnosis, to decrease community viral load and reduce the rate of new HIV infections. While this TasP approach will only be effective with scaling up of testing programs and ART adherence support, the recommendation that all pregnant and breastfeeding women living with HIV should initiate ART and remain on lifelong treatment regardless of clinical or CD4 stage of disease is a major breakthrough. For the first time, the ART strategy for pregnant women is fully aligned with the recommended first-line regimen for non-pregnant adults. Providing ART to all pregnant and breastfeeding women living with HIV serves three synergistic purposes: it improves individual health outcomes for mothers; it prevents mother-to-child transmission of HIV; and it prevents transmission of HIV from the mother to an uninfected sexual partner. The TasP approach holds enormous promise for women, their babies and their families.

The proportion of pregnant women living with HIV receiving ART more than doubled in 21 of the 22 Global Plan priority countries, from 36% in 2009 to 80% in 2015. Perhaps more importantly, 93% of pregnant women receiving treatment were prescribed lifelong treatment, up significantly from 73% in 2014.²¹⁰ There is broad theoretical support for universal treatment and many countries are committed to adopting a “Treat All” policy. But there are ongoing problems in resource-limited settings that must be addressed for successful implementation of these goals. For example, a recent report from China documents prolonged delay in repeat HIV testing in infants born to HIV(+) women; in two-thirds of infants, testing was delayed until after 18 months of age and by that time, one-third of the babies had died or were lost to follow-up.²¹¹

In 2016, there were 11.5 million women and girls living with HIV in eastern and southern Africa. On average, 76% of pregnant women living with HIV

had access to antiretroviral medicines to prevent transmission of HIV to their babies. There were 160,000 new HIV infections among children in 2016, down by 47% from ~300,000 in 2010.²¹² With optimized public health efforts, meaningful progress in preventing global mother-to-child transmission of HIV is within reach.

HIV/AIDS Prevention and Treatment: Global Status

- By the end of 2018, more than 74 million people have been infected with HIV and 32 million people have died of AIDS, a figure that threatens to eclipse the cumulative tens of millions who died in the 1918–1919 influenza pandemic, the gold standard for pandemic mortality.
- Globally, UNAIDS statistics report that 37.9 million people – 0.8% of the world's population – were living with HIV at the end of 2018.²¹²
- Prevalence varies widely from well below that level in countries like the United States to at least 10% of the population in eastern and southern Africa. In 2017, there were 19.6 million people living with HIV (53% of the world's total) in eastern and southern Africa, 6.1 million (16%) in western and central Africa, 5.2 million (14%) in Asia and the Pacific, and 2.2 million (6%) in Western and Central Europe and North America.²¹³
- Sub-Saharan Africa, which bears the heaviest burden of HIV/AIDS worldwide, accounts for 65% of all new HIV infections. Other regions most significantly affected by HIV/AIDS include Asia and the Pacific, Latin America and the Caribbean, and Eastern Europe and Central Asia.
- In the last several years, Russia has been the country with the largest number of new HIV cases and AIDS deaths. In January 2016, Russia reached its millionth case of HIV with currently at least 850,000 people living with HIV; a large number of these individuals are unaware of their diagnosis.²¹⁴
- Gains in treatment are largely responsible for a 50% decline in AIDS-related deaths globally, from an estimated 2 million in 2005 to 1.5 million in 2010 and 1.1 million in 2015.
- By the end of 2015, mean global coverage of antiretroviral therapy reached 46% with the greatest gains in the world's most affected region, eastern and southern Africa, where mean coverage increased from 24% in 2010 to 54% in 2015, reaching a regional total of 10.3 million people.²¹⁵

If even the current rate of progress can be sustained, there is potential to end this global pandemic. UNAIDS and the ONE Campaign reported that in 2013, a tipping point was reached in the fight against the disease when the number of people newly added to treatment that year was more than the number of people newly infected with HIV. If the number of people on treatment continues to increase and the number of new infections continues to decrease, we can theoretically end the HIV/AIDS epidemic in the next 15 years.²¹⁶

Looking Back :: Moving Forward

HIV infection is responsible for one of the most devastating human pandemics of all time, but its story is also one of enormous scientific accomplishment. Against formidable odds, 5 years after recognition of the first cases, the epidemiology of the disease had been described, the causative virus had been identified, the pathophysiology of the disease was recognized and a test to diagnose infection had been developed. For those who lived through this time when thousands of people died tragically and horribly, this progress must have felt discouragingly irrelevant and interminably slow, as a diagnosis of AIDS was still, essentially, a death sentence. It was not until 1996 that development of combined treatment with antiviral medications proved to be effective for treatment of AIDS and for control of HIV infection. The advent of effective antiretroviral therapy (ART) dramatically changed the course of the pandemic, transforming HIV infection into a treatable chronic disease and saving millions of lives. This was followed by demonstration that if viral load is effectively suppressed in HIV(+) individuals, the virus is no longer transmissible. But HIV infection is still not curable. Future progress focuses on maximizing delivery of known, effective treatment and development of a definitive preventive and curative strategy.

Despite the enormous progress made since the first AIDS cases appeared, even antiretroviral therapy is still far from perfect. Treatment adherence is a powerful predictor of survival for individuals living with HIV infection, with an established required level for effective viral suppression of 95%. Despite development of new, potent antiretrovirals and once-daily, single-pill treatment regimens, average individual adherence to antiretroviral therapy is far below that, varying from 27% to 80% across different populations. In terms of treatment, only 19.5 million of the 36.7 million HIV-infected people in the world are receiving ART at all and viral suppression is reportedly achieved in less than half of these.²¹⁵ Even achieving the goals of “treatment as prevention” is well-nigh impossible, requiring identification of all HIV-infected individuals, provision of effective, lifetime anti-HIV medication and viral suppression in treated individuals to undetectable levels. We are far from achieving any of these goals, with an estimated 15% of all HIV-positive Americans and 44% of young people in the 13–24-year-old age group unaware of their diagnosis. This proportion is at least as large in other parts of the world. In response to statistics like these, scientific strategies to combat HIV/AIDS have developed in four major areas: virus eradication; new approaches to prevention and treatment; reduction of structural barriers to diagnosis and treatment; and vaccine development.

- The major biologic barrier to HIV eradication is latency, the persistence of integrated replication-competent HIV reservoirs in memory CD4+ T cells which emerge whenever ART is stopped. The most studied approach for eliminating latently infected T cells is based on the “shock and kill” theory, where a latency-reversing agent is used to flush out the reservoirs and then a cytolytic agent clears the latent viruses.^{217–219} Research directed at every stage of

this process is ongoing, from the development of biomarkers to quantify HIV persistence to engineering T cells to eliminate HIV-infected cells to enhancing the capacity of an individual's own immune system to clear HIV-infected cells. There is also intense interest in gene therapy primarily focused on CCR5, the cofactor for HIV cell entry.

- Women urgently need more options for HIV prevention. Currently available forms are limited, and many women are unable to negotiate condom use or ART with male sexual partners or access to pre- or post-exposure prophylaxis. A new option currently in clinical trials is a vaginal ring which continuously releases the anti-HIV drug dapivirine. This was designed to be a discreet, long-acting HIV prevention option for women with the wearer replacing the product herself every 4 weeks. In an open-label study of women in southern and eastern Africa, the dapivirine vaginal ring reduced the risk of HIV infection by 39%, according to statistical modeling.²²⁰
- To address well-documented problems with treatment adherence, researchers have developed an ultra-long-acting, tunable, biodegradable and removable polymer-based delivery system. After subcutaneous placement in an animal model, this new delivery option was shown to provide sustained plasma concentrations of six antiretroviral drugs for periods up to one year. A safe, removable, long-lasting injection system like this will take away the burden of adhering to a daily medication regimen and transform HIV/AIDS treatment.²²¹
- With clear demonstration that ART significantly improves the health of HIV(+) individuals and dramatically reduces HIV transmission, social and behavioral research is focusing on known structural barriers to effective ART by increasing diagnosis rates, treatment initiation and viral suppression in at-risk populations. In 2016, UNAIDS established the “90–90–90” global targets, aiming to have 90% of HIV-infected people identified, 90% of those with HIV infection receiving antiretroviral treatment, and 90% of those on treatment achieving undetectable viral levels by 2020. Mathematical models show that universal HIV testing followed by immediate ART could theoretically eliminate viral transmissibility, effectively ending the almost 40-year-long global HIV/AIDS pandemic.²²²
- Two recent studies show the potential power of effective interventions directed at structural barriers to prevention and treatment. A community-based testing and treatment program in rural Kenya and Uganda used a public campaign to establish annual HIV testing linked to universal ART access and facilitated care for HIV(+) individuals. After two years, the 2020 goals had been achieved with 95.9% of HIV(+) individuals identified, 93.4% on ART, and 89.5% of those virally suppressed.²²³ A randomized trial compared standard ART initiation following weeks after HIV testing to same-day HIV testing and ART initiation in eligible adults ≥ 18 years old in Port-au-Prince, Haiti. In the standard group, ART was initiated a mean of 3 weeks after HIV testing. At 12-month

follow-up, significantly more of the same-day ART initiation group were retained in care and had appropriate viral suppression.²²⁴

- Efforts to develop a vaccine to prevent or modify HIV infection have been ongoing since the late 1980s, stymied primarily by the extravagant capacity of the virus for mutation which results in great genetic diversity, with multiple strains and subtypes prevalent in different parts of the world, and by the existence of replication-competent virus reservoirs. In 2000, the HIV Vaccine Trials Network (HVTN) was established, linking a network of 25 clinical sites in the United States, Africa, Asia, South America, and the Caribbean dedicated to developing a preventive HIV vaccine by testing and evaluating candidate vaccines in all phases of clinical trials. To this time, results have been limited, but there are two ongoing trials: in 2009, the RV144 trial in Thailand led by the US Military HIV Research Program showed their investigational vaccine to be 31% effective in preventing HIV infection – the best result for any HIV vaccine thus far.²²⁵ In November 2016, the HVTN 702 study was launched, testing a vaccine based on the RV144 vaccine in more than 5000 adults in South Africa. The HVTN 702 regimen includes two experimental vaccines: a canary pox vector-based vaccine called ALVAC-HIV and a two-component gp120 protein subunit vaccine with an adjuvant designed to enhance the body's immune response to the vaccine. Launched with great hope, the study was closed on February 3, 2020 after the experimental vaccine was shown to have had no efficacy – there was no difference in the HIV infection rate between people receiving the vaccine and people receiving a placebo.²²⁶ Despite this very discouraging failure, further vaccine efforts will undoubtedly follow.
- On November 30, 2017, multiple international partners including the NIH and the Bill & Melinda Gates Foundation announced the HVTN 705/HPX2008 study of an investigational HIV-1-preventive “mosaic” vaccine. The mosaic vaccine was computationally designed from protein sequence data extracted from a database of more than 800,000 HIV sequences. The computer code used to design the vaccine was inspired by the way HIV-1 itself naturally evolves. The study will evaluate whether the investigational vaccine regimen is safe and able to reduce the incidence of HIV infection among 2600 sexually active women in sub-Saharan Africa.^{225–227}

Extraordinary scientific achievements mark the current understanding of HIV/AIDS as it has evolved from a universally fatal global pandemic with no identified agent and no treatment to a treatable chronic disease theoretically associated with a normal lifespan. New approaches addressing all aspects of care hold the potential to end the current pandemic and prevent future infection. From the outset, the nature of the virus has characterized the disease: the secrets to any curative strategy lie in a complete understanding of the capacity of this unique virus to produce acute and persistent infection.

I wanted to end this chapter on a positive note – after all, the progress made has been impressive and ending the HIV pandemic by virus eradication or complete global suppression seems almost within reach. But one Sunday, I was reading the obituaries in the *New York Times* when a headline leapt out at me: *Michael Friedman, Co-Creator of 'Bloody, Bloody Andrew Jackson' Dies at 41*. The article confirmed what the headline already told me – the cause of death for this “versatile, cerebral and witty composer and lyricist” was complications of HIV/AIDS.

I cannot remember the last time I read an AIDS obituary like this, but I can easily remember a time when there were at least several every Sunday. Of course, in the early days – through the 1980s – no one explicitly identified AIDS as the cause of death. The small type read something like “after a long illness,” with only parents and siblings listed as survivors. “Donations in his memory to God’s Love We Deliver.” Or ACT UP. Or Bailey House. Or rarely, the Gay Men’s Health Crisis. The number of talented young men who died of AIDS in those years was overwhelming. Right at that time, a friend told me about his “Triscuit Index” – based on his grandfather’s advice, he had been following the status of the stock market by checking the price of Triscuits every year on his birthday. I had already been keeping a rough mental tally of AIDS obituaries in the *Sunday Times* and I began to think of it as the “AIDS Inventory” – a personal way to keep a handle on one small corner of the epidemic. Over the years, it proved to be a surprisingly accurate reflection of the evolution of the AIDS epidemic in NYC. In the early 1990s, the Inventory numbers peaked, reflecting the fact that at that time, AIDS was the leading cause of death for men in New York City between the ages of 25 and 44. As time passed, the men who died gradually became older. Sometimes they were survived by a life partner. And eventually, the cause of death was actually given as “complications of AIDS.” After 1996 when antiretroviral therapy became widely available, the numbers dwindled and then seemed to disappear.

I hadn’t thought of the AIDS Inventory in many years, but Michael Friedman’s death notice brought that terrible time right back. The last line of his obituary reads, “His death stunned the theater community which had lost many artists to AIDS in the 1980s and ‘90s but fewer in recent years.” In the days that followed, there was a memorial service and some details of Michael’s illness emerged. He had reportedly been working very hard in the preceding 6 months, opening a new children’s musical in Minnesota while simultaneously acting as the artistic director of *Encores! Off-Center!*, an annual summer program at New York City Center. Friends noticed he had lost weight and even the appearance of small purple lesions on his face, but he was not tested for HIV until 9 weeks before he died, when he presented with full-blown *Pneumocystis pneumonia*. Antiretroviral treatment was started immediately, but despite all efforts, he died.

How did this happen? A gay man in NYC, the first identified high-risk AIDS group; a man who worked in the theater, the community that had suffered the greatest losses to AIDS in the early years of the epidemic; a man with many HIV-positive friends on treatment – *this* man had not been tested for HIV for at least several years. Here I am writing about programs to increase HIV testing and treatment in the southern United States and in sub-Saharan Africa and right here in NYC, a gay man is not diagnosed with HIV until he presents with AIDS, just weeks before he dies. No matter where in the world we live, all the amazing treatment advances of the last 25 years are useless without proactive testing and early diagnosis.

Yes, there has been great progress – and yes, there is still more work to be done.

HISTORIC PERSPECTIVE: THE POWER OF ACTIVISM

The federal public health network discussed in the section on influenza failed most profoundly when it was faced with HIV. The virus hit humans where we are least capable of changing and most constrained by prejudice: sex. The first group to be identified as victims of the disease was gay men, to such an extent that it was originally identified as Gay-Related Immune Deficiency (GRID) before the cases linked to IV drug use and blood transfusions rendered this label inaccurate and obsolete. Because this group of people was not granted equal rights as citizens by every member of the United States Congress, a view that was representative of the country at the time, funding AIDS research became a political football. In 1987, Senator Jesse Helms of North Carolina famously led his House of Congress in passing an amendment to an appropriations bill that prevented funding of AIDS education programs (that were proven to be highly effective) by the Centers for Disease Control because they might “promote, encourage, or condone homosexual activities.” Only two senators, Daniel Patrick Moynihan and Lowell Weicker, voted against this amendment, which essentially starved federal funding for AIDS prevention. Where the government failed, however, independent organizations succeeded. Due to the tireless efforts of the Gay Men’s Health Crisis, ACT UP, and other groups around the country, HIV/AIDS rates among gay men fell precipitously within 5 years. These organizations also provided care for those affected, funded research, and defended the civil rights of AIDS patients and their partners. In an era when being gay was still accepted as a rationale for discrimination, these individuals declared war on the federal government and its elected officials who refused to recognize their rights to privacy or the critical importance of a centralized education effort to prevent the spread of this terrible disease.

Gay Men's Health Crisis (GMHC) formed in 1981 in New York City in response to what was then considered "gay cancer." It was called that in response to the CDC warning about the sudden proliferation of the relatively rare cancer, Kaposi's sarcoma, among gay men. CDC researchers and others would quickly notice the correlation between KS, *Pneumocystis carinii* pneumonia, and other immune deficiencies among gay men and rename the disease GRID. Larry Kramer and about 80 other gay men met in his living room to discuss raising funds for research. Their efforts to inform gay men about HIV transmission and the critical importance of condom use over the next 6 years directly contributed to Jesse Helms' hateful amendment.²²⁸ By 1982, GMHC opened the first AIDS hotline, a telephone that rang in a volunteer's New York City apartment and fielded over 100 calls the first night.²²⁹ In 1983, they funded the first AIDS discrimination lawsuit, which was brought by the Lambda Legal Defense and Education Fund.²³⁰ New York's gay men had every reason to organize: they were in an epicenter of the AIDS epidemic, there was little accurate information about the disease available to the general public, and AIDS patients consistently faced discrimination by healthcare professionals. They met before the CDC declared the disease an epidemic (also in 1981) and over a year before AIDS research received any federal funds. In 1982, the CDC still was not sure women could get AIDS, although cases associated with blood transfusions and IV drug use would quickly change that misperception.²³¹ The men who founded the GMHC met because their lovers and friends were dying, and nobody seemed to care. Some were even openly happy, claiming the disease was divine vengeance against homosexuals. Gay people in New York City had already demonstrated the power of activism in the first wave of the gay rights movement beginning with the Stonewall Riots, and the gay activist network in New York City was strong, identifiable, and relatively wealthy. Using their existing network for fundraising and community support, GMHC produced educational material that would become the foundation for AIDS prevention, provided daily help to people with AIDS in New York City, created a vital legal bulwark against AIDS discrimination, and funded research into effective treatments. This is an extraordinary example of an identifiable community of people uniting to create a self-funded public health response based on education and awareness, and it is a model of how to create an effective community response to a public health threat. When GMHC began its work, condom use among gay men was very rare. Long before it was proven to be an effective deterrent to AIDS transmission (1988), condom use among gay men had increased to such an extent that in 1988 in New York City, more new cases were attributed to intravenous drug use than sex.²³² The fact that the majority (two thirds) of new cases were also among African American men points to the slow acceptance of homosexuality in the

African American community and one of the areas in which the GMHC was least effective: bridging the racial gap in the gay rights movement.

The GMHC did three things exceptionally well: it produced educational material about HIV and its transmission and distributed it within the gay community, to healthcare workers, and to the general public; it raised enormous amounts of money to support people with AIDS and provided care for them, as well as legal defense when necessary; and it made AIDS part of popular culture through theater and film, as well as part of political culture by appearing before Congress, insisting on Constitutional protection for people with AIDS, and demanding funding for research and education. While President Reagan was still insisting against all evidence, in 1986, that there was no reason for the general public to worry about AIDS because it only affected gay men and drug users, Larry Kramer's "A Normal Heart" had been on stage for a year and "An Early Frost," a television film featuring a main character with AIDS, had already aired.²³³ The importance of making AIDS and AIDS patients visible to the public cannot be overlooked, especially as gay activism was much harder to find outside of large cities. Ryan White, the teenage hemophiliac from Indiana who died of AIDS at 18 after facing extreme discrimination for his condition, has been credited with making AIDS patients "victims" rather than sinners who deserved their fate, but a great deal of credit for making AIDS victims visible and human also goes to Kramer and other writers, such as Paul Monette (*Borrowed Time: An AIDS Memoir*, 1988), who put them on stage and in readers' hands where their humanity could not be denied.

For all the incredible work GMHC did and continues to do, however, it could not prevent the epidemic spreading across the world. The version of the virus that reached North America might have been a direct import from Haiti, but it also had deep roots in sub-Saharan Africa. In an increasingly global world, diseases travel faster than the human response to them. But it is worth remembering that a group of men who fit in a living room founded a movement that fundamentally changed their world – and ours – for the better. Activism matters. Because if Paul Monette wrote, "It will be recorded that the dead in the first decade of the calamity died of our indifference," he also declared, "Grief is a sword."²³⁴

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7

OUT OF NOWHERE

West Nile Virus, SARS, Zika, and Ebola



FIGURE 7.1 Electron micrograph of the Ebola virus.

Source: cdc.gov

A Hopeful Ebola Warrior

At the end of September 2014, I retired as a Professor of Pediatrics at the University of Rochester. October was my first month without full-time employment in the last 40 years, a simultaneously liberating and terrifying situation. One morning in that first week, I was drinking coffee and reading the *New York Times* at 10 o'clock in the morning – a previously unknown experience. The Ebola epidemic ravaging West Africa was front-page news with 2400 deaths since the first reported case in the outbreak in December 2013 in Guinea. President Obama had just announced a major, military-led US response to the Ebola outbreak that “has reached epidemic proportions and now poses a potential threat to global security.” Every channel was covering the epidemic 24/7, reporting that medical volunteers were desperately needed. All of a sudden, I realized this was something I could do, a way I could put all my years of medical experience to work. Online, the US Agency for International Development (USAID) had the following announcement:

MEDICAL VOLUNTEERS

If you are a qualified medical professional and want to volunteer to work in West Africa assisting those affected by the Ebola outbreak, please fill out the form embedded below to submit your contact information to USAID's Center for International Disaster Information.

I filled out the form the same day. According to the USAID website, all applications from experienced health-sector workers would be reviewed and triaged to different agencies like the CDC, Project Hope, and Médecin Sans Frontières. Volunteers would be contacted within the next 2–4 weeks to arrange training and posting. I was tense but elated, ready to go. I reassured my anxious husband and was congratulated by my adventurous daughter. I began reading everything I could get my hands on about Ebola and identified the vaccinations I would need to enter West Africa. Every day, I checked the website for updates and my email for responses. Two weeks later, I received a very polite and extremely dismissive email reporting that because individuals over 59 years of age have a worse outcome if they contract Ebola, no volunteers in my age group were being accepted. I tried emailing and calling to no avail. My career as an Ebola fighter was over.

But my interest in Ebola was not. Initial recognition of this terrifying hemorrhagic fever occurred more than 40 years ago when simultaneous outbreaks occurred in two small villages in central Africa. From the outset, Ebola hemorrhagic fever was seen to have an extremely high fatality rate, more than 50% of all clinically apparent cases – one of the highest mortality rates of any known

infectious disease. But previous outbreaks had occurred in localized small populations and had typically burned themselves out within months when the virus could find no new subjects to infect. The pandemic that began in Sierra Leone was different and galvanized scientists, ID specialists, and public health practitioners – like me – all over the world.

Studying the Ebola pandemic as it evolved sparked the realization that epidemics caused by viruses have been increasing in frequency and ferocity over the last century. Terrifying disease outbreaks caused by new and re-emerging viral pathogens – like Ebola – have been occurring at closer and closer intervals. Often, the virus has jumped from an animal reservoir to infect humans and equally often, the virulence of the pathogen has been initially underappreciated. Historians have identified recurrent themes that have marked almost every pandemic beginning with the plague in the thirteenth century: the sudden emergence of a previously unknown disease; the critical role of travel bringing a new contagion to a naïve population; the importance of poor general health and hygiene, overcrowding and lack of sanitation; and inadequate access to appropriate healthcare. But as with the Ebola pandemic of 2014–2015, our response to each new epidemic – the response of the scientific and medical establishment and the general public – almost always includes a sense that the outbreak sprang “out of nowhere!” In fact, the most recent global epidemic challenges with West Nile virus, SARS, Ebola, and the Zika virus did expose new elements that have made us increasingly vulnerable to infectious threats: emerging viral pathogens; ever-increasing world population density with chaotic urbanization; rapid, frequent global travel and trade; and environmental change. Each epidemic originally did seem to emerge from nowhere to blast its way through the virology and epidemiology and disease characteristics that we thought we knew to create a terrifying narrative all its own. Each was originally a mystery illness and as the narratives in this chapter will show, how quickly we responded by identifying and containing the pathogen was directly measured in lives lost or compromised. The stories are unique, but identifying the critical connections between the power of new viral contagions and global interconnectedness illuminates the terrifying capacity for deadly disease outbreaks in our current toxic environment. How rapidly we identify and how effectively we respond to viral disease outbreaks like these may well be critical factors in our survival as a species.

Out of Nowhere: West Nile Virus, SARS, Zika, and Ebola

I. West Nile Virus

The dead birds came first. Near the end of June 1999, residents of northern Queens, one of New York City’s five boroughs, began to find bodies of dead birds, most

often crows. From early July, officials at the Bronx Zoo received daily calls about dead birds and the zoo's chef pathologist, Dr. Tracey McNamara, became concerned about a potential pathogen that could infect the zoo's exotic bird collection. After a summer of "dead bird" calls, her concern was tragically realized in early September when two Chilean flamingoes, an Asian pheasant, and a cormorant died suddenly over a 3-day period. Autopsies of the dead birds revealed signs of brain inflammation and bleeding along with myocarditis, with no recognized pathogen. By this time, there had been many, many citizen reports of dead birds in Manhattan, Westchester, and Connecticut. Dr. McNamara sent specimens from the zoo's cases to the National Veterinary Services Laboratory in Ames, Iowa and to the CDC in Atlanta, with initially no conclusive identification of the pathogen. Finally, she sent new specimens to the US Army Medical Research Institute of Infectious Diseases in Iowa, where flavivirus-like particles were observed by electron microscopy.¹ These were forwarded to the CDC, where West Nile virus was identified on September 21.² At the time, West Nile virus was a virus known to cause encephalitis, but it had never previously been identified in North America, nor reported to cause disease in birds.

Meanwhile, on August 23, an infectious disease specialist at Flushing Hospital in Queens contacted the NYC Health Department to report two elderly patients admitted with similar serious signs of encephalitis, an inflammation of the brain, with no identifiable cause. Over the next 2 weeks, seven new cases were admitted from the same area with similar alarming neurologic findings, including signs of axonal neuropathy with flaccid paralysis like that seen with polio; three elderly patients died.³ When an environmental investigation was performed, all the patients were found to have come from the same area in Queens and all were avid appreciators of the outdoors. Mosquito breeding sites were identified in the yards and/or neighborhoods of every patient. Urgent CDC evaluation of blood and spinal fluid samples using antibody testing originally led to identification of St. Louis encephalitis virus, a neurotropic virus known to cause encephalitis but never previously seen on the east coast. Subsequently, DNA sequencing of viral isolates by polymerase chain reaction (PCR) analysis led to the identification of West Nile virus (WNV) as the cause of this cluster of encephalitis cases.⁴ By September 28 when knowledge of the two parallel outbreaks converged, there had been countless avian WNV infections and deaths, and a total of 17 confirmed and 20 probable human cases of WNV encephalitis with four deaths reported from NYC and surrounding counties. A serious outbreak was underway.

The Disease and the Vector Identified

WNV was first isolated in 1937 from the blood of a febrile Ugandan woman during yellow fever surveillance screening.⁵ That first patient's only symptom was fever, but subsequent serologic studies with injection of her serum into mice led to isolation of a virus similar to two flaviviruses known to cause encephalitis – St. Louis encephalitis virus and Japanese B encephalitis – suggesting that this new

virus might also be neurotropic.⁶ The early pattern of clinical illness associated with WNV infection was defined in the 1950s when there were a series of outbreaks in the biogeographic region bordering the Mediterranean Sea. At that time, WNV fever was described as a generally mild flu-like illness with symptoms of fever, headache, myalgia, rash, and vomiting. No fatalities or encephalitis cases were recorded in these early outbreaks.^{7,8}

Studies in the 1940s demonstrated that WNV was carried by mosquitoes, suggesting vector-borne transmission. Detailed serologic and ecologic studies in humans and animals conducted by the US Naval Medical Research Unit with the Ministry of Public Health in Egypt in the early 1950s were the first to define the basic ecology and epidemiology of WNV infection.⁹ The virus was found to be widely disseminated in the populations of the Nile Delta with clinical disease consistently described as a mild, flu-like illness with no cases of encephalitis and no fatalities. However, experimental infection of humans with terminal cancer (performed to induce a theoretically beneficial febrile reaction) did lead to several cases of encephalitis, proving the WNV did have neurotropic properties. Viremia developed by 24 hours after infection and lasted up to 12 days, with the duration correlating with the severity of the illness. Besides mosquitoes, a number of additional hosts were also identified including camels, cows, donkeys, water buffalo, goats, horses, sheep, and bats; horses often developed severe, symptomatic infections which could be fatal. Extensive studies of captured arthropods showed WNV only in mosquitoes, predominantly the *Culex* species. Multiple avian species including crows, herons and pigeons were found to be positive for WNV. On the basis of these studies, *Culex* mosquitoes were identified as host vectors for WNV with birds as reservoir hosts. Humans and domestic quadrupeds were thought to be only incidentally infected. This was the first identification of the primary “bird–mosquito–bird” cycle of WNV.

In 1957, during a widespread outbreak of WNV in Israel, the first naturally occurring cases of encephalitis were reported in a group of elderly patients and over the next 20 years, rare cases of encephalitis were reported in a series of WNV outbreaks in Europe, Africa, Russia, and India.^{7,10}

Until the 1990s, large outbreaks of WNV were rare and the disease was consistently mild, but the epidemiology appeared to change with epidemics of increasing size and severity beginning with a large outbreak in Bucharest, Romania in 1996. The clinical spectrum was different, with a reported preponderance of cases with central nervous system (CNS) involvement – encephalitis or meningitis. In contrast to previous outbreaks which occurred where WNV disease was common and serologic evidence suggested widespread background infection, the Romanian population was largely serologically naïve to WNV and therefore highly susceptible to the infection.¹¹ This epidemic was followed by a series of widely disseminated, sporadic WNV outbreaks with significant CNS involvement and higher fatality rates in sub-Saharan Africa, the Middle East, Europe, Southern Asia, India, China, and the Far East, thought to be spread by migrant birds originating in northern Africa.^{12,13}

Until 1999, the Western Hemisphere was spared, but that summer, multiple factors converged to bring the WNV to NYC. It is not known exactly how the virus entered the United States – it could have been carried by infected humans or pets, by imported or migratory birds, or by virus-infected mosquitoes.¹⁴ But however the virus traveled here, its arrival certainly reflected the importance of increased global connectivity in the spread of infections. The speed of spread and the extent of this new epidemic reflected the complete absence of immunity in both birds and humans in North America. The summer of 1999 was also the hottest and driest summer in a century and scientists believe the heat may have accelerated the breeding cycle of the *Culex* mosquito vectors and the replication rate of the virus during digestion. In that first outbreak, active surveillance ultimately identified 62 patients, 59 of whom were hospitalized, all with laboratory evidence of recent WNV infection and clinical evidence of CNS involvement; 10% of patients had diffuse flaccid paralysis with findings compatible with an axonal polyneuropathy. Extrapolating from this surveillance group, the attack rate of clinical WNV infection in the outbreak was reported to be at least 6.5 cases per million population. The overall case fatality rate was 12%, but among patients with muscle weakness it was much higher, reported to be 30%.¹⁵ Even before the West Nile virus was confirmed as the cause, the outbreak provoked an extensive regional public health response with a telephone hotline to answer questions and leaflets and public messages on radio and television, warning the public to take precautions against mosquito bites. NYC distributed insect repellent at fire houses and for the first time began to spray pesticides in areas where there was evidence of WNV activity, using aircraft in the outer boroughs and trucks in the streets of Manhattan.

The actual number of WNV infections in 1999 is impossible to determine, but it is estimated to be many thousands of people. Birds were known as a reservoir for the virus – this was the first reported WNV outbreak in which birds developed evidence of disease with many thousands of avian deaths primarily in crows and jays before the epidemic ended after fall frosts suppressed mosquito populations.

The Virus, the Reservoir, and the Vector

After its original identification, serologic cross-reactivity studies identified WNV as a member of the Flaviviridae family in the genus *Flavivirus*, within the Japanese encephalitis serocomplex, along with the Japanese encephalitis virus and the St. Louis encephalitis virus.² WNV is often classified functionally as an arbovirus, a group of pathogens linked by mosquito or tick vectors as transmitters, and shared seasonal incidence and geographic distribution determined by the transmitting vectors. While other viruses can cause encephalitis, only arboviruses have caused epidemics of viral encephalitis.¹²

WNV is a small, spherical, single-stranded, positive-sense RNA virus with a lipid bilayer envelope. By cryo-electron microscopy – evaluation of ultra-thin frozen slices – it is seen to have icosahedral symmetry and a smooth surface with no visible

projections or spikes.¹⁶ The RNA genome encodes a single polyprotein which is cleaved into three structural proteins which form the capsid, membrane, and envelope, and seven multifunctional, non-structural proteins which are important for viral synthesis and/or assembly, and modulate cell signaling and immune responses. The complex processes of viral attachment and cell entry remain the subject of ongoing investigation. Unlike other RNA viruses, WNV has a slow mutation rate with changes occurring almost exclusively by genetic drift.¹³

By phylogenetic analysis of published isolates, five distinct WNV genetic lineages have been identified, with lineages 1 and 2 associated with disease outbreaks in humans. Lineage 1 has three clades: clade 1a includes isolates from Africa, Europe, the Middle East, Russia, and the Americas – the strain identified in the 1999 NYC outbreak is part of this clade; clade 1b contains the Kunjin virus from Australia; clade 1c contains only isolates from India. Distribution of clade 1c is documented as far back as the early 1800s. Lineage 2 is found in isolates from sub-Saharan Africa, Madagascar, and Russia. Lineages 3 and 4 have been isolated from potential vectors but have never been identified in association with human disease. By phylogeographic analysis, the most recent common ancestor of WNV 1a is thought to have originally emerged in Africa around 1921.^{13,17}

In the 1999 NYC epidemic, genome sequencing of the virus from the brain of one of the two dead Chilean flamingoes and isolates from other bird species plus two human cases revealed identical genetic sequences, confirming that a single WNV strain caused the outbreak in both humans and birds. By phylogenetic analysis, the NYC WNV strain – termed NY99 – showed a very high degree of sequence similarity, greater than 99.8%, with a clade 1a Israeli virus isolated from a dead goose in 1998. Retrospectively, that same strain had previously been observed to be associated with disease in birds, but this had never been reported in any WNV outbreak. Thus, the cause of the NY99 outbreak was originally thought to be a single WNV strain introduced from Israel.^{7,14} Subsequent phylogeographic analysis indicates that the WNV strain from Israel and the NY99 strain plus several others now circulating in Europe actually originated from the same independent, unknown location, probably in Africa. Of note, all these strains are associated with avian mortality, supporting the concept of their common origin.¹⁷

Consistent with the original findings in Egypt in the 1950s, mosquitoes remain the natural vector for WNV transmission with at least 65 species identified as potential transmitters in the United States. Solely ornithophilic mosquitoes infect only birds and maintain the enzootic cycle between birds and mosquitoes, but they do not infect humans. Mosquitoes who feed on both birds and humans are called bridge vectors because they can carry the virus from the infected avian reservoir to incidental mammalian hosts – humans and domestic vertebrates. Mosquitoes from the *Culex* genus are the most important WNV bridge vectors in North America, Europe, Australia, and South Africa, with different *Culex* species dominating transmission in other areas.¹³

Among the hundreds of bird species shown to carry the WNV, passerine or “perching” birds are the primary reservoirs and infecting hosts because they develop

high enough levels of viremia to efficiently infect mosquitoes. Certain birds – especially, crows, jays, and robins – are called WNV amplifiers because they are favorite mosquito targets with high levels of viremia. Humans, horses, and other domestic mammals can experience serious – even deadly – disease, but they do not develop high enough serum virus levels to infect mosquitoes and are therefore known as dead-end hosts.^{12,18} In North America, WNV infections occur in prime mosquito season, from July to September. When an infected mosquito bites a susceptible human host, components in the mosquito's saliva suppress the immune reaction at skin level. Infected skin cells then migrate to draining lymph nodes from which systemic viremia develops, carrying infection throughout the body and potentially to the CNS.¹²

The Disease, Updated

Over time, the contemporary clinical pattern of WNV infection has been clarified. As with polio and yellow fever, 75–80% of individuals infected with WNV are entirely asymptomatic. Approximately 25% develop a mild, self-limited, flu-like illness with some combination of fever, myalgias, headache, lymphadenopathy, and truncal rash. A much lower percentage (less than 1%) experience potentially devastating neuroinvasive manifestations, with the likelihood of this kind of neurologic involvement increasing significantly with age. Symptoms of meningitis due to WNV are similar to those seen with other viral meningitides, namely fever, headache, and photophobia with neck pain and stiffness. Signs of WNV encephalitis range from mild, transient confusion to severe encephalopathy with multiple kinetic symptoms, coma, and death. Very rarely, acute, flaccid paralysis develops, secondary to anterior horn cell involvement; this dreaded pattern can result in quadriplegia and respiratory failure. The majority of patients with uncomplicated WNV fever or meningitis recover completely, but the prognosis for those with encephalitis is variable, with more than a third reporting some residual symptoms at one year post infection. In patients with acute flaccid paralysis, one third recover completely, one third have some improvement, and one third have little or no improvement with time. Among those individuals who develop clinical neurologic disease, the case fatality rate ranges from 4% to 13%, and across outbreaks is consistently highest among elderly patients over 70 years of age.^{12,19}

While mosquito bites account for the vast majority of human WNV infections, the virus has also been transmitted by transfusion with infected blood and blood products and by heart, liver, lung, and kidney transplant.¹³ Blood donor screening with nucleic acid amplification testing has dramatically decreased the risk for transfusion-related WNV infection in North America, but every year, blood from several hundred asymptomatic donors tests positive for WNV and rare cases of post-transfusion disease occur.^{20,21} Transplacental transmission can occur but is extremely rare, with no definitive evidence of consequent fetal abnormalities. Peri-partum transmission has also been reported.

Diagnosis, Treatment, and Prevention

Because of its non-specific presentation, WNV fever can be difficult to diagnose. Even with clinical signs of meningitis or encephalitis, specific testing for WNV has been reported in less than half of cases, so a high index of clinical suspicion is necessary.²² If WNV infection is suspected, detection of IgM antibody in serum or spinal fluid by MAC-ELISA testing is the standard diagnostic test. Because only approximately 50% of the typical minimally symptomatic patients have ELISA testing at clinical presentation, testing of acute and convalescent sera is often needed for definitive diagnosis of WNV fever. By contrast, 90% of patients with signs of involvement of the CNS are positive for IgM antibodies in spinal fluid within 8 days of symptom onset. In uncertain cases, nucleic acid testing for virus-specific genetic material – the technique used to screen the donor blood supply – can be used.

Treatment of WNV infection remains supportive because none of a variety of theoretically useful measures including antiviral agents, WNV recombinant humanized monoclonal antibody, and polyclonal gamma-globulin infusions have been proven effective.²³

Development of a safe and effective vaccine has been a major research focus. Approaches include vaccines containing cocktails of individual WNV proteins, chimeric vaccines which combine genes from more than one virus into a single vaccine, and DNA vaccines, in which DNA that codes for a particular WNV protein is combined with bacterial DNA with the combined product injected directly into the skin of the vaccinee. Currently, there is no licensed WNV vaccine for people although several have been tested in preliminary clinical trials. In 2005, the US Department of Agriculture licensed a DNA vaccine to prevent equine WNV, and since then, at least four other types of WNV vaccines have been approved for use in horses.

There are barriers to developing a human vaccine against an unpredictable disease like WNV with varying outbreak size from year to year, including safety concerns and the risk that manufacturers who carry a vaccine all the way to a Phase III trial may not recoup their investment. Researchers had predicted prospects for a vaccine being developed were low unless WNV became an uncontrollable global epidemic.²⁴ Funded by the National Institute for Allergy and Infectious Disease (NIAID), HydroVax-001 is a new WNV vaccine based on a novel, hydrogen peroxide-based process that renders the virus inactive while still maintaining key immune-system triggering surface structures. In a Phase I clinical trial the HydroVax-001 vaccine was found to be modestly immunogenic and well-tolerated at escalating dose levels.²⁵ Phase II trials are underway.

The other focus of prevention is directed at mosquito management with elimination of breeding sites and pesticides to reduce mosquito populations plus aggressive pesticide use during outbreaks. Public health programs recommend personal protection with protective clothing and insect repellent use against mosquitoes throughout the summer season.

After NYC

The WNV already had an impressive global distribution with multiple viral strains identified throughout Africa, the Middle East, southern Europe, western Russia and Asia, and Australia when the NYC outbreak occurred, but before the summer of 1999, no case of WNV disease had ever been reported in the Western Hemisphere. Astonishingly, from the original presentation in NYC in 1999, the virus spread across the entire continent to the Pacific Coast by 2003, to South America by 2005, and across Canada by 2009.^{26,27}

Since 1999, there have been annual summer outbreaks of WNV disease in the United States of varying size and severity with peaks of activity in 2002–2003, 2006, and 2012; each of these summer seasons were notably hot and dry. In 2002, a new WNV genotype, WN02, appeared, characterized by one amino acid substitution and 13 conserved nucleotide mutations. WN02 was found to be more efficiently transmitted by New World mosquitoes than the NY99 strain.²⁸ This genetic change coincided with large US outbreaks in 2002–2003 and may have contributed to the rapid spread of WNV across North America. A second new genotype termed SW/WN03, defined by two additional fixed amino acid substitutions, was first observed in isolates collected in 2003. Since that time, WN02 and SW/WN03 genotypes have completely displaced the ancestor NY99 genotype in the United States.²⁹ High but stable WNV activity in the US continued until the summer of 2012 when another large outbreak of WNV disease occurred, with 2873 reported neuroinvasive cases and 286 deaths. Because the majority of WNV-infected individuals are asymptomatic, incidence tracking is based on neuroinvasive disease where reporting is more complete. Based on this methodology, WNV is now endemic in the United States; yearly outbreaks have resulted in an estimated total of 4–5 million human infections! Between 1999 and 2014, over 41,700 cases of West Nile disease – the proverbial tip of the iceberg – have been reported to the CDC, including 18,810 neuroinvasive cases and 1765 deaths.^{29,30}

Distribution of West Nile virus is determined by a complex of demographic, environmental, and social factors. Increasing international travel and trade, rising population density, and progressive urbanization have facilitated global spread. Higher temperatures and lower precipitation rates related to climate change have made transmission seasons longer and more intense.³¹ Following its introduction to the United States in 1999, WNV has caused the three largest arboviral neuroinvasive disease outbreaks ever recorded with nearly 3000 cases each year in 2002, 2003, and 2012. Globally, there has been a continuous increase in WNV cases, most recently in Europe in the summer of 2018.^{12,32} Now found on every continent except Antarctica, WNV is a major global health problem with – to this time – ongoing, unpredictable regional, national and international outbreaks, no standardized method of prevention, and no effective therapy.

Looking Back :: Moving Forward

The introduction of West Nile virus (WNV) into North America in 1999 is a classic example of viral emergence in a new, naïve host environment. Subsequent dramatic dispersion across the continent reflects the impact the virus had on equally naïve bird populations accompanied by an established, widely distributed mosquito vector. Understanding the spread of this virus is an important step towards effective prevention. Phylogenetic analysis of the complete genomes of avian isolates sampled across the United States between 2001 and 2012 reveals a star-like tree structure, indicative of explosive viral spread with minimal replacement of viral genotypes over time.³³

Analysis of diffusion rates indicates that the spread of WNV occurred too quickly to be explained by simple contiguous spread, even with highly mobile avian reservoirs and mosquito vectors. The flyways of terrestrial birds including those that carry WNV are similar although distinct from those of waterfowl, like those that carry the influenza virus. There are three defined North American terrestrial bird flight paths – Western, Central, and Eastern – within which individual birds use looped routes that allow them to maximize tail winds and access feeding sites. Recent avian phylogeographic studies suggest that the flight paths of terrestrial birds like those that carry WNV are important components in the spread of the virus. This same approach identified optimal sites for WNV surveillance in New York, Illinois, and Texas.³⁴ Targeted surveillance and vector migration analyses based on information like this represent important potential ways to predict the annual flow of WNV and implement focused interventions. Indeed, a recently released network model that includes WNV spreading by migratory birds using established flyways shows potential for prediction of virus spreading in simulation models.³⁵

At least 75% of emerging and re-emerging diseases in the last half century are either zoonotic, vector-borne, or – like WNV – both. Such diseases emphasize the importance of interrelationships among humans, animals, and the environment in the emergence and diffusion of disease in our increasingly connected world. The *One Health Initiative* is based on this concept – that human, animal, and ecological health are inextricably linked.³⁶ No emerging disease narrative exemplifies this better than the arrival of WNV in New York where – out of nowhere – a previously unknown virus established host reservoirs in local bird flocks from which mosquito vectors perpetuated the infection, incidentally infecting naïve human hosts and spreading rapidly throughout the entire Western Hemisphere. It was a veterinarian caring for exotic tropical birds who first identified the virus and crow deaths have subsequently been shown to be a sensitive sentinel surveillance system for WNV.^{2,37} Direct collaboration between physicians, veterinarians, and epidemiologists to address the animal and human interface behind zoonotic outbreaks is an important approach to creation of effective treatment and prevention strategies at local, national, and international levels.

When WNV infection involves the central nervous system, morbidity and mortality are high, so development of effective therapeutic options is of critical

importance. Validation and standardization of prevention efforts are also a high priority. Effective surveillance systems to predict developing outbreaks are critical and lessons learned from experience with annual outbreaks in the United States and ongoing international research should facilitate development of such systems. Of equal importance is implementation of sustainable vector management at local, national, and international levels coupled with aggressive execution of adult mosquito control programs. Finally, development of a safe, cost-effective vaccine to prevent WNV infection is a global priority.

II. Severe Acute Respiratory Syndrome – SARS

In November 2002, multiple inhabitants of the Chinese province of Guangdong on the coast of the South China Sea suddenly developed symptoms of a flu-like illness with headache, fever, and dry cough. Over a period of approximately 5 days, some of these patients developed worsening cough and shortness of breath. In this subset of patients, chest x-rays showed signs of progressive air-space disease compatible with atypical pneumonia, but laboratory work was remarkable only for a mild increase in total white cells with low lymphocyte and platelet counts. In some patients in this group, respiratory distress progressed rapidly to respiratory failure and death. The illness spread through six municipalities, apparently carried through direct contact with sick individuals. On February 11, 2003, the Chinese Ministry of Health notified the World Health Organization (WHO) that 305 cases of this acute respiratory illness of unknown etiology had occurred between November 16, 2002 and February 9, 2003.³⁸ The report stated that the disease was particularly noteworthy for transmission to healthcare workers and household contacts; five deaths were reported in this group, important evidence of person-to-person transmission. Investigations had ruled out anthrax, pulmonary plague, leptospirosis, and hemorrhagic fever. By the time of China's report, the outbreak had been in progress for at least two and a half months.

This new disease spread very rapidly. On February 26, an American businessman traveling from China developed respiratory distress while on a flight to Singapore. The plane landed urgently in Hanoi, Vietnam and the traveler was hospitalized at the Vietnam French Hospital. Doctors there suspected a possible atypical influenza virus and contacted the local office of the WHO for assistance. This is where fate intervened in the form of Dr. Carlo Urbani, a specialist in infectious diseases who provided that consultation.³⁹ Dr. Urbani had extensive experience in global medicine as a former president of Médecins sans Frontières (MSF) and he immediately recognized the gravity of the illness and the potential for epidemic spread. He sent samples for emergent testing and created an isolation ward in the hospital to care for the growing number of cases who followed in the wake of the American traveler, half of whom were healthcare workers. The WHO responded with an emergency meeting with the Vietnamese Minister of Health and this led to city-wide infection control measures and an international appeal for assistance; experts from the CDC, WHO, and MSF responded and with traditional disease control methods – isolation

of sick individuals and quarantine of contacts – the Hanoi outbreak was brought under control. Tragically, Dr. Urbani himself became infected with the unknown pathogen and he died on March 18, 2003.³⁹

Almost simultaneously, an outbreak of a similar respiratory illness was reported in Hong Kong. In this cluster, the index case was a nephrologist working in a hospital in southern China who traveled to Hong Kong on February 21. He originally stayed in a hotel but developed progressive respiratory distress and was subsequently hospitalized. Despite intensive support including ventilation, he died. Between February 22 and March 22, 10 additional patients with SARS were immediately identified in Hong Kong. Most had social or hospital care contact with the index patient, but in at least one case, contact was at most very limited, confirming the highly contagious and infectious nature of this unknown disease pathogen.⁴⁰

There was an important international connection with this Hong Kong outbreak: a couple from Canada stayed at the same hotel on the same floor and at the same time as the index case described above.⁴¹ As far as could be determined, there had been no direct contact between them, but on February 25, two days after returning to Toronto, the 78-year-old wife developed fever, anorexia, and cough. Within 5 days, her cough worsened and she became progressively short of breath; she died at home 3 days later. Her 43-year-old son developed progressive symptoms beginning February 27 and despite intensive respiratory support, he died on March 13. It was at this point that the new Chinese respiratory illness was first considered as a possibility and four additional family members screened positive for possible or probable pulmonary compromise. Five additional contact cases were diagnosed, including the doctor who evaluated the index case in this outbreak and her husband, a man who was exposed to patient 2 in the hospital ED, and a man from Vancouver who stayed in the same hotel implicated in the Hong Kong outbreak. In this cluster of 10 cases, four people died and one was still in Intensive Care being ventilated at the time of the report. Subsequent contact tracing identified an additional 100 individuals with probable or suspected Severe Acute Respiratory Syndrome or SARS – the newly defined acronym – with one additional death reported. In addition to the description of the epidemiology of the cases, the Canadian report described virologic studies in the Toronto cases which identified a new, previously unidentified coronavirus in five and human meta-pneumovirus in four.⁴¹

With confirmation of a highly contagious, rapidly progressive, sometimes fatal viral pneumonia transmitted by direct contact, airborne droplets and fomites now reported in at least four countries, the WHO instituted worldwide surveillance on March 15, 2003 and issued a rare global travel alert about the outbreak as evidence mounted that this acute, atypical pneumonia was spreading by air travel along international routes. WHO named the mysterious illness after its symptoms: severe acute respiratory syndrome (SARS), and declared it “a worldwide health threat.”⁴² On March 21, 2003, the US Centers for Disease Control (CDC) provided an interim case definition.⁴³

CDC INTERIM CASE DEFINITION FOR SEVERE ACUTE RESPIRATORY SYNDROME (SARS) SUSPECTED CASE

Respiratory illness of unknown etiology with onset after 2/1/2003 and the following criteria:

- Measured temperature >100.4 degrees F (38 degrees C).
- One or more clinical findings of respiratory illness (e.g., cough, shortness of breath, difficulty breathing, hypoxia or radiographic findings of pneumonia or acute respiratory distress syndrome).
- Travel within 10 days of symptom onset to an area with suspected or documented community transmission of SARS.

OR

- Close contact within 10 days of symptom onset with either a person with respiratory illness and travel to a SARS area, or a person under investigation for SARS.

By March 26, a total of 1323 suspected and/or probable SARS cases including 49 deaths had been reported to the WHO from 14 different countries – a case–fatality ratio of ~4%. Chinese authorities reported an updated total of 792 suspected/probable cases and 31 deaths in Guangdong province between November 16, 2002 and February 28, 2003.

The Virus

On March 28, the CDC reported that a novel, previously unrecognized coronavirus had been identified in clinical specimens from two patients from Thailand with suspected SARS. The isolate was identified initially as a coronavirus by electron microscopy, corroborated by results of immunostaining, indirect immunofluorescence antibody (IFA) assays, and reverse transcriptase–polymerase chain reaction (RT-PCR) with sequencing of a segment of the polymerase gene. IFA testing of sera and RT-PCR analysis of clinical specimens from six other SARS cases were positive for the new coronavirus. Sequence analysis indicated that this new agent was distinct from all other known coronaviruses.⁴⁴

Other laboratories collaborating in the WHO-led investigation including the team from Canada had found similar results and had also isolated human metapneumovirus from some patients with suspected SARS.⁴¹ At that time, information was insufficient to determine what roles these two viruses might play in the etiology of SARS. By April 16, the WHO announced that the new pathogen, a member of the coronavirus family never before seen in humans, was confirmed as

the cause of SARS and would be designated as SARS-CoV.⁴⁴ The speed at which the virus was identified was the result of the close international collaboration of 13 laboratories from 10 countries. WHO and the network of laboratories dedicated their detection and characterization of the SARS virus to Dr. Carlo Urbani, the WHO scientist who first alerted the world to the existence of SARS and who subsequently died from the disease.^{45,46}

Coronaviruses belong to the subfamily Coronavirinae in the family of the same name. They are enveloped spherical viruses with a positive-sense single-stranded RNA genome. The size of the genome is the largest for any RNA virus, ranging from 26 to 32 kilobases. The name “coronavirus” is derived from the Latin *corona*, meaning crown, and refers to the characteristic appearance of the virus by electron microscopy which reveals a halo of spikes on the surface of the virus identified as S proteins.⁴⁷ These are the major antigenic determinants of coronaviruses, mediating receptor association and fusion of the viral and host cell membranes.

Coronaviruses are rapidly evolving viruses using the now familiar mechanisms of spontaneous point mutation and recombination to create ongoing genetic diversity. As a group, they cause respiratory and gastrointestinal disease in a wide variety of birds and mammals including cats, dogs, pigs, cows, chickens, and ferrets. In humans, coronaviruses are responsible for 30–60% of common colds. Until SARS-CoV, no identified coronavirus was known to cause lower respiratory tract illness.

During the initial SARS outbreak in China in 2002–2003, animals from a Guangdong live animal “wet market” were identified as the likely immediate source of infection because all the early cases had a history of animal contact in this location. SARS-CoV was isolated from a majority of Himalayan palm civets in the market and subsequent culling of palm civets dramatically reduced the number of other infected animals in the marketplace. However, while the majority of civets in the market showed evidence of SARS-CoV infection, civets on farms and in the wild were free of the infection, indicating that the market animals were only intermediate hosts for a virus that had first crossed species to infect them in the market setting, and then jumped to infect humans with whom the civets had direct contact.⁴⁷

Bats had already been recognized as the natural reservoirs for a large variety of diverse viruses, including more coronaviruses than any other species. In 2005, two independent research groups reported almost simultaneously the discovery of novel coronaviruses related but not identical to SARS-CoV in horseshoe bats in China. After years of investigation, a live SARS-like CoV very closely resembling human SARS-CoV was isolated from bat fecal samples and was neutralized by convalescent SARS patient sera, providing convincing evidence that Chinese horseshoe bats are the ancestral origin of SARS-CoV.⁴⁸ While direct transmission of bat coronaviruses to humans is rare, human activity increasingly allows overlap with intermediate hosts like the civet, which can mediate interspecies transmission.

Over the next 4 months, humans carried the SARS virus to 30 countries and areas of the world but it became deeply embedded in just six. In affected areas, approximately 20% of all cases were in healthcare workers. Ultimately, 8439 people

were infected and 812 died from SARS in the 2002–2003 outbreak.⁴⁹ There were four cases of confirmed SARS in Guangdong province in the winter of 2003–2004; all patients recovered. Since 2004, there has never been another identified case of SARS.

Looking Back :: Moving Forward

SARS presented emergent requirements to the global health system and despite concurrent outbreaks in multiple locations, these were met by a remarkable international collaboration coordinated by the WHO and the CDC. In the 5 months following the first cases of SARS in China, the epidemiology of this previously unknown disease was described and a novel causative organism identified.^{45,46} Using a secure Internet site, laboratories shared information about the disease and the virus in real time. SARS-CoV was shown to be accurately diagnosed using enzyme-linked immunoassays (EIA) or RT-PCR tests, performed on respiratory secretions or blood. Classic disease control measures – active surveillance, early diagnosis, hospital infection control with isolation, contact tracing with quarantine, and international reporting – were aggressively implemented in multiple sites and proved effective. While a wide variety of antiviral and anti-inflammatory measures were attempted, there were no conclusive benefits so aggressive supportive care was the recommended approach.⁵⁰

On July 5, 2003, the World Health Organization removed Taiwan, China, from the list of areas with recent local transmission of SARS, the last area to be cleared. Based on country surveillance reports, the chain of SARS-CoV transmission had been broken everywhere in the world.⁵¹ There have been no identified cases of SARS since 2004.

The SARS pandemic showed us how quickly a previously unknown virus can emerge from an animal reservoir and spread in our increasingly populous, highly mobile and interconnected world. This outbreak also emphasized the consequences of delayed reporting of a new disease outbreak – in the almost 3 months after the first cases appeared in China, the virus was able to establish a major outbreak there. There was extreme under-reporting of the number of cases, the severity of the illness and its spread within China, and this initially minimized the importance of the outbreak and, therefore, the global response. Chinese authorities continued to cover up the extent of the outbreak for months before a brave whistle-blowing physician, 72-year-old Jiang Yanyong, exposed the crisis through western media, galvanizing the global response that ended the SARS pandemic. More recently Jiang, now 88, has had his contacts with the outside world cut off and movements restricted after he asked the authorities to reassess the 1989 Tiananmen pro-democracy movement. He is now under de-facto house arrest.

Despite this delay, the SARS pandemic did show how concerted international cooperation and disease containment measures could allow health experts to effectively eliminate international spread of a highly contagious and virulent new disease. There has never been a better demonstration of the power of global collaboration.

III. ZIKA Virus

The discovery of the Zika virus, like the West Nile virus, was an incidental finding: while taking samples as part of routine yellow fever surveillance in the tropical forests of Uganda in 1947, scientists isolated a new virus from captive sentinel rhesus monkeys. Named Zika virus (ZIKV) for the Ugandan forest in which it was first identified, the virus was also recovered from an *Aedes africanus* mosquito on a tree platform in that same forest, suggesting vector-borne transmission.⁵¹ In 1952, serological surveys in Uganda and Nigeria showed Zika antibodies in 75% of a sample population, suggesting widespread unrecognized infection. The first definitive evidence that the virus could cause clinical illness in humans appeared in 1954 when a 10-year-old Nigerian girl with fever and rash showed a post-symptom rise in antibodies against ZIKV.

Over the next 40 years, the Zika virus was repeatedly detected in mosquitoes and monkeys used for yellow fever research in a narrow band of countries stretching across equatorial Africa. During that same time period, ZIKV migrated from Uganda to West Africa and then to Asia along with infected humans and mosquitos, with occasional cases of mild human illness detected along the way. The geographical distribution expanded to include India, Pakistan, Indonesia, and Malaysia where sero-prevalence studies indicated widespread population exposure but reports of overt disease remained mild and rare. During this time, the close resemblance between ZIKV, dengue, and chikungunya in clinical disease symptoms and in viral characteristics was observed and confirmed.⁵² In 2007, the pattern changed abruptly when the Zika virus caused a large disease outbreak on the tiny Pacific island of Yap, located in the Philippine Sea, due north of Papua New Guinea.⁵³ Given the island's isolated location in the open ocean and the complete absence of monkeys, the virus is thought to have been carried to this naïve population by an infected person or an accidentally imported mosquito. Based on house-to-house surveys, 73% of Yap's 7391 citizens were infected with the Zika virus during this outbreak. Although there were no deaths, hospitalizations or severe complications reported, the dramatic size and rapid spread of the outbreak were remarkable, attributed to a combination of lack of population immunity and mis-identification/under-reporting of cases in previous outbreaks.⁵³

By this time, we thought we had a reasonable knowledge base about the Zika virus and ZIKV infection: ~80% of those infected were completely asymptomatic. The vast majority of those with symptoms had a very mild illness characterized by low-grade fever and headache associated with a non-specific itchy rash and mild, generalized body aches. The rash began on the face and spread throughout the body. There was conjunctivitis (inflammation of the eyes) in approximately 60% of cases. In the absence of complications, recovery occurred in 4–7 days.⁵⁴ The primary mode of transmission was via the bite of *Aedes* mosquitoes – especially *A. aegyptius* and *A. aldopictus* – encountered previously by us as the agents for transmission of yellow fever. Infection with Zika virus is generally suspected based on symptoms and recent history of travel to an area with active Zika virus transmission. Specific,

accurate diagnosis is difficult because antibody response to related flaviviruses like dengue is cross-reactive, and antibody detection of ZIKV is therefore non-specific in populations previously exposed to any of the four dengue viruses or West Nile virus, and/or vaccinated against yellow fever virus. The definitive diagnosis of ZIKV infections has therefore increasingly depended on detection by nucleic acid tests. Laboratory evidence of a confirmed recent Zika virus infection is therefore quite complicated, requiring either detection of Zika virus or Zika virus RNA or antigen in any body fluid or tissue specimen; or a positive or equivocal Zika virus or Dengue virus IgM test on serum with a positive titer for Zika virus (≥ 10) from plaque reduction neutralization testing (PRNT) and a negative PRNT titer for dengue virus. Similar to other flavivirus infections, Zika virus IgM antibodies can remain in the body for months after infection, making it difficult to use serologic tests to determine the timing of infection. A completely dependable, accurate and responsive diagnostic test for rapid confirmation of ZIKV diagnosis in the field has yet to be developed.⁵⁴

The Virus

The Zika virus (ZIKV) is a member of the Flaviviridae virus family and the genus *Flavivirus*, and is thus directly related to the dengue, yellow fever, Japanese encephalitis, and West Nile viruses.⁵⁵ Like other members of the genus, Zika virus is enveloped and icosahedral and has a non-segmented, single-stranded, 10-kilobase positive-sense RNA genome, first sequenced in 2007. The RNA genome encodes seven non-structural proteins and three structural proteins including the flavivirus envelope glycoprotein, which initiates viral entry by endocytosis by binding to the endosomal membrane of the host cell.

In 2012, genetic researchers constructed phylogenetic trees using Zika virus strains collected in Africa (Uganda, Nigeria, and Senegal), and Asia (Cambodia, Malaysia, and Thailand). Two geographically distinct lineages were identified – Asian and African – with multiple strains within each lineage.⁵⁶

After the island-wide outbreak on Yap, there were sporadic cases of Zika virus infection reported from several countries in South-East Asia between 2010 and 2013. In 2013, the story changed again when there was a huge outbreak of ZIKV disease involving more than 28,000 people in French Polynesia. Serologic testing showed 66% of the population had been infected. French Polynesia is more than 5000 miles across the open sea from Yap Island in the middle of the South Pacific Ocean, but near-identical nucleotide sequencing indicates that the viral strain causing the outbreak was of Asian origin and originated from Yap Island. Given the distance between the two sites, the virus could only have been imported by an infected person.⁵⁷

It was during this large outbreak that ZIKV disease was first observed to be associated with Guillain-Barré Syndrome (GBS), a rare, serious autoimmune disease of the nervous system in which an individual's immune system attacks the

myelin sheaths of peripheral nerves. The condition often develops a few days or weeks after a viral infection with rapid onset of neurological symptoms which can progress from a tingling sensation in the extremities to paralysis of the muscles that control breathing. Patients respond to treatment with immunoglobulins or to plasma exchange but the mortality rate is 5%. During the Zika epidemic in French Polynesia, the incidence of GBS was estimated to be 20-fold higher than its baseline island incidence.⁵⁸ Ninety-eight per cent of patients with GBS were shown to have antibodies against ZIKV, compared with only 55% of controls, strongly supporting a causative association.⁵⁹

Meanwhile, in east central South America, Brazil was enjoying a time of relative infectious disease tranquility following the successful anti-mosquito campaigns of the last century. With yellow fever apparently vanquished, those mosquito control programs had been largely dismantled. Infectious disease threat response shifted from building basic public health infrastructure and capacities for prevention as the first line of defense to the use of surveillance to pick up early signals of an outbreak and then mounting an emergency response. It was in this setting that doctors in north-eastern Brazil first began seeing patients with a characteristic disease pattern in the summer of 2014: almost all had the same symptoms of fever, bloodshot eyes, flat, pink, itchy rash, and headache. Dengue was very common in this area and the symptoms were similar, but serological tests excluded dengue as well as chikungunya. Although patients were not severely ill, their numbers were alarming and after investigation, authorities confirmed that the previously unknown disease was an ongoing outbreak of Zika fever, proven by RT-PCR by researchers from Brazil's Federal University of Bahia in May 2015. Zika had never previously been seen in South America. Local authorities linked the outbreak to the recent increased flow of foreign visitors prompted by a series of sporting events, coupled with the large population of the mosquito vectors, *Aedes aegypticus* and *A. albopictus*, that inhabit the region.⁶⁰

At first, doctors and epidemiologists were reassured by this information because Zika was thought to cause only mild symptoms in a minority of infected individuals. But within weeks, there was a spike in cases of GBS as seen in the ZIKV outbreak in French Polynesia.

And Then – Out of Nowhere

Then, late in the summer of 2015, doctors began to report large numbers of newborns with microcephaly in north-eastern Brazil associated with a maternal history of rash suggesting possible infection during the pregnancy.⁶¹ Microcephaly is an exceedingly rare anomaly caused by under-development of the brain; the baseline incidence is ~2–7 cases per 10,000 newborns. Microcephalic babies almost always have profoundly delayed development as well as other neurologic problems like seizures, vision abnormalities, and deafness. It has been reported after maternal exposure to teratogenic compounds and to maternal gestational infection with cytomegalovirus, rubella, herpes, or toxoplasmosis.⁶²

Case numbers accumulated rapidly and by November 2015, the Brazilian Government declared a national public health emergency.⁶³ A suspected association between maternal ZIKV infection and congenital microcephaly in their offspring then emerged from a retrospective analysis of the Zika disease outbreak on French Polynesia: serological and surveillance data found the baseline prevalence of microcephaly was 2 cases per 10,000 neonates compared with 95 cases per 10,000 women infected with Zika in the first trimester during the Polynesian outbreak.⁶⁴

Between November 2015 and June 2016, 7830(!) suspected cases of microcephaly were reported to the Brazilian Ministry of Health. From this group, 1500 infants were medically investigated with a strong association established between maternal history of rash during pregnancy and subsequent microcephaly. Infants with definite or highly probable ZIKV infection had severe intracranial calcifications and other major neuroimaging abnormalities including cortical malformations, ventriculomegaly, cerebellar hypoplasia, and abnormal hypodensity of the white matter. Many definite or probable cases of ZIKV syndrome were found to have normal head circumferences despite specific neuroimaging findings and laboratory evidence of ZIKV infection. Over time, a congenital Zika syndrome (CZS) was characterized with distinctive brain development abnormalities including some combination of microcephaly, intracranial calcifications, retinal manifestations, and defects of the extremities including congenital contractures and hypertonia.⁶⁵

The striking increase in congenital microcephaly and other neurological abnormalities in north-east Brazil was so concerning that the WHO declared the Zika epidemic to be a Public Health Emergency of International Concern on February 1, 2016, the very rarely used designation that was put into effect late in the 2014–2015 Ebola epidemic.⁶⁶ However, the potential spread of the Zika virus across the Americas and the possibility that a mosquito bite during pregnancy could cause such devastating neurologic damage in a developing fetus was so concerning that the declaration was felt to be justified. Over the next year, epidemiologic, pathologic, and biologic evidence accumulated supporting a strong association between prenatal ZIKV infection and congenital microcephaly with associated severe brain anomalies and ultimately, it was concluded that this was a direct causal relationship.^{67–71} *Birth defects resulting from a virus transmitted by a mosquito bite had never been previously reported.*

In response to confirmation of vertical transmission of ZIKV infection during pregnancy, countries including Brazil, Colombia, El Salvador, and Jamaica advised their populations to postpone planned pregnancies, to control mosquito populations by reducing mosquito-breeding grounds; and to prevent mosquito bites in at-risk individuals, especially pregnant women. Mosquito transmission was still considered the primary mode of infection but human sexual transmission by vaginal, anal, or oral sex, and the sharing of sex toys was subsequently confirmed. Zika was found to be transmitted sexually even if the infected person was entirely asymptomatic at the time.⁷² In response, the US Centers for Disease Control developed specific

recommendations to prevent maternal ZIKV infection, including: avoidance of travel to areas where ZIKV infection has been reported by women who are or plan to become pregnant; specific mosquito bite prevention efforts by pregnant women and their male and female partners who live in or travel to ZIKV-active areas plus use of sexual protection for the length of the pregnancy; testing for ZIKV infection in the first and second trimesters of pregnancy for women who live in ZIKV-active areas; and delayed attempts to conceive for 8 weeks for women and 6 months for men after travel to ZIKV-affected areas.

As it turned out, we knew relatively little about the Zika virus at the outset of the outbreak in Brazil, given its low profile and what we thought was minimal pathogenicity. The sudden and enormous number of ZIKV cases and the recognition of severe associated complications led to intense efforts to understand the dynamics of the epidemic and the pathophysiology of the infection.

Two hypotheses dominated investigation of the mechanisms responsible for the dramatic emergence of Zika virus as an epidemic pathogen with serious associated effects: the chance introduction of a virus with under-appreciated neurotropic characteristics into a large, immunologically naïve population with abundant *Aedes aegypti* mosquito vectors; or spontaneous adaptive genetic evolution enhancing human infection. Either or both mechanisms could theoretically result in enough severe ZIKV infection outcomes for definitive recognition of previously unrecognized outcomes.⁷³

Comparative genomic and phylogenetic analyses identified several amino acid substitutions that may contribute to increased ZIKV transmission and pathogenicity. Specifically, a spontaneous amino acid substitution in one of the virus' non-structural proteins has been identified in all clinical isolates from the Americas after 2013 but not from Cambodia back in 2010. The mutation increases ZIKV acquisition by mosquitoes from an infected mammalian host – and increased viral prevalence in mosquito vectors could have contributed to the rapid spread in the recent pandemic.⁷⁴

Using molecular mapping and next-generation sequencing, an international group of researchers explored spread of the Zika virus in the Americas. With a mobile genomics laboratory, they generated ZIKV genomes including one sequence from the earliest confirmed case of ZIKV infection in Brazil. Analysis of these viral genomes combined with ecological and epidemiologic data showed introduction of ZIKV into Brazil in February 2014, more than 12 months prior to the first report of clinical Zika infection in May of 2015. The projected date of origin coincides with a documented increase in air travel to Brazil from ZIKV endemic areas, specifically the Pacific Islands including French Polynesia. This is critical information because it indicates the virus was circulating in human and mosquito populations causing subclinical and unrecognized disease and the subsequently identified serious neurologic complications for more than a year before it was recognized.⁷⁵ As with HIV, delayed identification of an outbreak allows for exponential epidemic spread. With ZIKV, this was accelerated by the complete

absence of immunity to ZIKV in the enormous, immunologically naïve population of Brazil.⁷⁶

Another international study examined ZIKV genomes from clinical and mosquito samples from 10 countries and territories. Their phylogenetic analysis showed rapid expansion of the outbreak after the original introduction into Brazil with multiple subsequent introductions of ZIKV strains into Puerto Rico, Honduras, Columbia, other Caribbean islands, and then the continental United States. Again, ZIKV was found to have circulated undetected for many months in every location before the first locally transmitted cases were recognized.⁷⁷

Using phylogenetic trees from human and mosquito-derived genomes in Miami, researchers found evidence that Zika was introduced into Florida on multiple occasions, several months before it was detected. Their analyses suggested that ZIKV entered the United States from Caribbean countries, which are linked to Miami by extensive air and cruise-ship travel. The presence of *A. aegypti* mosquitoes coincident with large numbers of people arriving from high-incidence Zika areas supported successful introduction of the virus resulting in reported sporadic cases, but the transmission rate was below the threshold level needed to establish an ongoing epidemic.⁷⁸

Appropriately, the most intense contemporary focus of ZIKV research has been around the consequences of vertically transmitted infection during pregnancy. A retrospective analysis of clinical and postmortem findings in nine infants with definite intrauterine ZIKV infection confirmed the strong predilection of the virus for fetal CNS cells, corroborating experimental in-vitro and in-vivo studies of neural specificity with ZIKV infection during pregnancy.⁷⁹

One genetic mutation in the region coding for the ZIKV envelope protein is rare in African isolates but is consistently identified in all isolates from recent outbreaks. A recombinant ZIKV clone which contained this motif was highly pathogenic and lethal in a mouse model; by contrast, a recombinant clone in which this motif was deleted or mutated was highly attenuated and non-lethal with very limited replication in the brain of infected animals. These findings suggest that specific genetic changes in the ZIKV envelope protein are an important factor in ZIKV virulence and neuroinvasion.⁸⁰

The absence of reported microcephaly in outbreaks before 2013 led researchers to search for a mutation that made the virus more virulent to the fetal brain. Chinese scientists investigated the in-vivo neurovirulence of three contemporary ZIKV strains (VEN/2016) isolated in 2015–2016 and compared these to their Asian ancestral strain isolated in Cambodia in 2010 (CAM/2010) in 1-day-old neonatal mice, comparable to human fetuses in the third trimester. Upon intracerebral injection, all three contemporary strains led to profound neurological signs followed by 100% mortality, compared with death in only 17% of the CAM/2010-injected animals. Using an established mouse embryonic microcephaly model, the researchers then compared the effects of the contemporary and ancestral strains. Both viruses predominantly targeted neural progenitor cells, but the VEN/2016 strain was much more virulent, causing a more significant microcephaly phenotype

in the embryonic mouse brain. Based on these preliminary findings, the researchers compared the genome sequencing in the contemporary ZIKV strains, using the ancestral strain as a reference. Phylogenetic analysis revealed that the contemporary strains had accumulated multiple nucleotide substitutions. In particular, a single serine to asparagine substitution in the viral polyprotein substantially increased ZIKV infectivity in both human and mice neural progenitor cells and led to more significant microcephaly in the mouse fetus and higher mortality in neonatal mice. Evolutionary analysis indicated that the S139N substitution arose before the 2013 outbreak in French Polynesia when microcephaly was first reported. The substitution has been stably maintained during subsequent spread to the Americas. This adaptation makes ZIKV more virulent to human neural progenitor cells, and could have contributed to the increased incidence of microcephaly in recent ZIKV pandemics. While this work has not been universally accepted, it strongly suggests a spontaneous ZIKV genetic mutation may underlie the development of microcephaly during first trimester maternal ZIKV infection.⁸¹

Researchers in Brazil identified a striking difference in the incidence of microcephaly at different times and locations in the ongoing epidemic. During the first massive wave of ZIKV infection in north-east Brazil in the spring and summer of 2015, the peak monthly occurrence of microcephaly was very markedly elevated at 49.9 cases per 10,000 livebirths. The second wave of Zika virus infection was much smaller but involved all regions of Brazil from September 2015 to September 2016 and the occurrence of microcephaly was much lower with estimated monthly peaks ranging from 3.2 to 15 cases per 10,000 livebirths. The explanation for these differences is unknown, but could include the intensity of the Zika virus outbreak and the success of public health efforts to protect pregnant women from ZIKV infection.⁸²

Information is accumulating about the incidence of Zika-associated birth defects in pregnant American women with laboratory evidence of Zika infection. Among 442 completed pregnancies in the US through 2016, 6% of all fetuses or infants had evidence of Zika-associated birth defects, primarily microcephaly and other brain abnormalities. With definite first-trimester Zika infection, the prevalence was higher: 11% had evidence of Zika-associated birth defects.⁸³ Of the 250 pregnant women in the US who had confirmed Zika infection in 2016, 10% had a fetus or baby with Zika-related birth defects. This report is the first to provide analysis of a subgroup of pregnant women in the US with clear, confirmed test results of Zika virus infection.⁸⁴ By December 2017, there were 1297 confirmed cases of Zika infection during pregnancy in women in the USA.

A report from the ZODIAC study, a long-term follow-up of children born with Zika-related microcephaly, describes the health and developmental effects of congenital Zika virus infection in children with microcephaly through 2 years of age. At a mean age of 19–24 months, more than half have severe health and developmental problems in multiple areas including seizures, profound motor delay with spasticity and inability to sit independently, difficulties with sleeping and feeding, and hearing and vision problems.⁸⁵

Epidemic Spread

Wide distribution of *Aedes aegypti*, the principal vector of the virus, and other *Aedes* species has greatly facilitated the spread of the disease. As we learned with yellow fever, *A. aegypti* is an invasive mosquito species that has adapted well to densely populated urban environments. In addition to mosquito transmission, male-to-female human sexual transmission has increasingly been demonstrated in the US and elsewhere. The globalization of the Zika virus was made possible by the widespread presence in various parts of the world of *Aedes* vectors and increased human travel that facilitated geographic spread. This globalization of Zika follows that of West Nile, Ebola, dengue, and chikungunya. Its ultimate spread is difficult to predict, but will hopefully be restricted through vigorous preventive measures. On the recommendation of its Emergency Committee on Zika Virus and Observed Increase in Neurological Disorders and Neonatal Malformations, WHO issued a group of recommendations to contain the epidemic.⁸⁶

After the explosive onset of the epidemic in Brazil, it spread regionally and then globally, beginning with the Caribbean Islands and Mexico, and then into the United States, especially Texas and Florida, then Europe, India, the Far East, and Australia – essentially, all over the globe. According to the Pan American Health Organization/World Health Organization, 48 countries and territories in the Americas have confirmed transmission of Zika virus disease through mosquitoes since 2015 and five countries in the Americas have reported sexually transmitted Zika cases.⁸⁷ Some 250,000 cases have been confirmed, more than half from Brazil, and there were 2618 children born with confirmed congenital syndrome associated with Zika virus infection, again, most in Brazil. Extrapolating from reported cases, by 2016, more than 1.5 million people were estimated to be infected in Brazil alone.

Since 2016, when Zika was declared by the World Health Organization as a Public Health Emergency of International Concern, the virus has become established in more than 80 countries, infected millions of people, and left many babies with the collection of birth defects known as congenital Zika syndrome. Travelers have been confirmed as important sentinels of Zika virus transmission throughout the pandemic.⁸⁸

Then, almost as suddenly as it began, the number of new cases of Zika fever began to fall precipitously. On November 19, 2016, the WHO announced that the Zika virus was no longer a “Public Health Emergency of International Concern” but should be considered a dangerous mosquito-borne disease like malaria or yellow fever with long-term efforts needed to address the virus.⁸⁹

Researchers who reconstructed the temporal spread of ZIKV in Salvador in north-eastern Brazil where the disease was first identified have shown the most likely explanation for the end of the epidemic. Using specimens sampled from before, during and after the outbreak, they showed that ZIKV seroprevalence (antibody prevalence in the population) increased from 4.2% in 2013 to 17.4%

in 2015, and to 63.3% by the end of 2016. Based on modeling projections, ZIKV reached the critical community protective immunity threshold – herd immunity level – within a single year. These results predict restricted ZIKV spread in the area until new, susceptible individuals are added to the population. This is compatible with the complete absence of reported, new ZIKV cases in the Salvador area since 2016.⁹⁰ This projection for future ZIKV cases is also compatible with the results of stochastic spatial modeling of Zika transmission, which also predicted the end of the current epidemic within 3 years with herd immunity delaying future large epidemics for a decade or more.⁹¹ Those predictions are being borne out in real time as the number of new cases of Zika fever has continued to decrease dramatically in South America, Central America, and the Caribbean since mid-2016. Per the Pan American Health Organization, since epidemiological week 44 of 2016, no additional countries or territories of the Americas have confirmed vector-borne transmission of Zika virus disease. Compared with more than 205,000 probable cases in 2016, Brazil had reported only 13,253 cases as of July 2017.⁹²

In 2016, the United States recorded 224 probable or confirmed locally transmitted cases in Florida and Texas – in 2017, there was just one local transmission in Texas. The dramatic epidemic that began in 2015 had almost vanished.⁹³ Given the high community protective immunity threshold – the protective herd immunity we described in the polio chapter – a new epidemic in the next decade is very unlikely. Zika virus is believed to have been maintained primarily in nature in a sylvatic cycle of transmission between non-human primates and forest-dwelling mosquitoes, just like yellow fever. This could allow future outbreaks to occur as susceptible population groups appear, but there is no evidence this pattern has been established in the Americas to this time.

Alternatively, the Zika virus could transition to persistent endemic circulation in the human population, with the virus maintained continuously at low levels; in this scenario, sustained transmission would result in the need for ongoing surveillance and prevention efforts directed against the severe complications associated with infection. Understanding the long-term epidemic potential of the Zika virus in the Western Hemisphere is a work in progress.

Prevention

There is no treatment for primary Zika infection and none is needed given the minor symptoms it produces. However, in light of the major neurologic and congenital complications, effective preventive measures are of critical importance. Aside from the personal protective efforts recommended by the CDC and the WHO, research strategies for prevention of a global pandemic have focused on vector control programs and effective vaccine development.⁹⁴

Traditional vector control measures like insecticides and elimination of larval breeding sites are still recommended, but one new approach involves the development of mosquitoes that are resistant to arbovirus infection. The bacterial symbiont *Wolbachia* has been transferred from *Drosophila* into the mosquito *Aedes aegypti*, where it blocks the transmission of arboviruses including Zika. Mosquitoes

infected with *Wolbachia* were resistant to current circulating Zika virus isolates with reduced virus prevalence, intensity, and disseminated infection.⁹⁵ A *Wolbachia*-infected *A. aegypti* mosquito has been developed and has already been shown to spread through mosquito populations after large-scale release. *Wolbachia*-infected mosquitoes were released in two Rio de Janeiro neighborhoods in 2014, and in a suburb of Medellín in 2015. Researchers plan to survey the insects for viral infection and track the local incidence of disease in areas with and without *Wolbachia*-infected mosquitoes. Proving that *Wolbachia* infection of wild mosquitos limits human infections will be critical before the method can find widespread use.⁹⁶ A field trial in Townsville, Australia has eliminated local arbovirus disease transmission over more than 2-year follow-up.⁹⁷ The World Mosquito Program is reportedly testing this approach in 12 countries.

As with yellow fever, another alternative is the development of a genetically modified *A. aegypti* mosquito which expresses a repressible lethal gene. Male mosquitoes are mass-reared in insect nurseries (a fascinating concept!) where they are given tetracycline as a dietary additive – tetracycline suppresses the activation of the lethal gene. After release, these mosquitoes compete with wild males to mate with females. Offspring carry the lethal gene and do not survive to become adults because they have no access to tetracycline. Known as RIDL for Release of Insects carrying Dominant Lethal genes, this approach is undergoing field testing. A field release of RIDL mosquitoes in Bahia, Brazil reportedly achieved a 95% reduction in local mosquito populations.⁹⁸

The association of Zika virus infection with congenital microcephaly and GBS has resulted in accelerated vaccine development efforts. Based on prior flavivirus vaccine development programs, multiple vaccine strategies have already advanced to the stage of clinical evaluation. These include nucleic acid (DNA and messenger RNA), whole-inactivated virus, live-attenuated or chimeric virus, and protein or virus-like particle vaccines. Within a year from the declaration by the World Health Organization of Zika virus as a Public Health Emergency of International Concern, multiple vaccine candidates entered clinical trials, with additional candidate vaccines in preclinical development.⁹⁹ One NIH vaccine candidate, the VRC's investigational DNA vaccine, was created on a platform initially developed for a West Nile virus vaccine. In only 4 months, this vaccine was in a Phase I clinical trial and it has now advanced to a Phase II/Ib trial in Texas, Puerto Rico, South and Central America.^{100,101} An experimental Zika vaccine lowered levels of virus in pregnant monkeys and improved fetal outcomes in a rhesus macaque model of congenital Zika virus infection. This rapid progress in vaccine development demonstrates the global capacity to respond to pandemic threats when the need is great and emergency funding is made available. However, the dramatic fall in Zika cases will make it difficult to complete clinical vaccine trials.

Looking Back :: Moving Forward

The Zika virus is the latest infectious disease to demonstrate the combined limitations of medicine and science to respond to an emergent viral threat. After

more than half a century as a covert cause of trivial disease, the enormous numbers of cases of ZIKV disease in this pandemic revealed serious and previously unrecognized neurologic complications when the virus was introduced into a large, immunologically unprotected population. Fortunately, collaborative global research has begun to increase our knowledge of Zika pathogenesis and transmission, exemplified by two 2018 research reports.

- A study of nonhuman primates infected with Asian/African ZIKV in early gestation showed fetal demise in 26% of the animals without clinical signs of infection. The results suggest that pregnancy loss due to asymptomatic ZIKV infection may be a common but under-recognized adverse outcome of maternal ZIKV infection.¹⁰²
- Cryo-electron microscopic single-particle reconstruction of the ZIKV at a resolution of 3.1 Å revealed heretofore unseen glycoprotein interactions and surface properties of the virus. Compared with other mosquito-borne flavivirus structures, the largest structural differences and sequence variations were seen to occur at the glycosylation loop associated with receptor binding, potential sites for drug development and vaccine design.¹⁰³

At the same time, the extraordinarily high infection rate has created powerful herd immunity, eliminating new ZIKA infections at the present time. The intense ongoing research focus on ZIKV disease outcomes and on disease prevention through vector control programs and facilitated vaccine development engendered by the global spread of this “new” pathogen will hopefully result in an improved capacity to respond when the next viral disease emergency strikes.

IV. Ebola

In the summer of 1976, there were two separate, near simultaneous outbreaks of a terrible illness in central Africa. Members of two small isolated communities – Yambuku in Zaire’s tropical rainforest in the northern frontier, and Nzara in the grasslands of southern Sudan – suddenly began developing fever, headache, joint and muscle pain, sore throat, and intense weakness, followed by stomach pain, diarrhea, vomiting, and rash. Many developed red eyes (due to conjunctival injection), hiccups and then signs of bleeding, from the nose, mouth, and GI tract. The fatality rate was high with many deaths in both locations. Within days, family members and care providers began to fall ill with the same symptoms. Calls for help to Kinshasa, the capital of Zaire brought the medical director for the zone to Yambuku where he found a scene of near panic with multiple desperately ill villagers and members of the local Belgian missionary group, the only source of health care in the area. His report led the Minister of Health to place the whole Bumba Zone around Yambuku under strict isolation and urgently request help from the CDC to determine the cause of the outbreak. Reports of the similarly

devastating outbreak in southern Sudan sent health workers to collect samples from patients there as well.¹⁰⁴

Under the direction of the WHO, blood and tissue samples from both outbreaks were sent to high-security laboratories in multiple locations for analysis. In Belgium, preliminary tests excluded yellow fever and typhoid – both considered possibilities – but under the electron microscope, the blood samples were found to contain a previously unrecognized virus with a long, curled, worm-like shape, as shown in Figure 7.1.¹⁰⁵ At the CDC in the United States, the microbiology team confirmed that finding, reporting that the illnesses in both locations were caused by a new, previously unrecognized virus that resembled the Marburg virus, a known cause of hemorrhagic fever.¹⁰⁶ In response, the WHO issued two urgent bulletins describing the outbreaks of hemorrhagic fever in northern Zaire and south Sudan caused by a new virus, morphologically similar to Marburg virus but antigenically different.¹⁰⁷ The virus was named Ebola, after the Ebola River in Zaire near which the disease was first recognized.

On the ground in both locations, the number of new cases gradually decreased over approximately 2 months and then stopped. A full-scale epidemiologic survey of the outbreak in northern Zaire reported that there had been 318 cases of the new viral disease and 280 were fatal, an alarmingly high mortality rate of 88%.¹⁰⁸ Investigation of the Sudanese epidemic found 284 cases with 151 deaths, a mortality rate of 53%.¹⁰⁹ Secondary cases were relatively rare, occurring only in those who had extensive direct contact with confirmed patients, so the virus was not thought to be highly transmissible. Despite investigations in both locations, the origin of the Ebola virus was not identified. The WHO report of the Zaire outbreak concludes with this prophetic description: “No more dramatic or potentially explosive epidemic of a new viral disease has occurred in the world in the past 30 years.”¹⁰⁸

After that impressive and alarming start, there was a long, unexpected hiatus with no Ebola outbreaks recorded for almost 15 years. During the interval, biologic studies of the virus from the Sudan and Zaire epidemics showed the original outbreaks were caused by two different subtypes of the virus, subsequently called Ebola Zaire and Ebola Sudan.¹¹⁰

In 1990, there was a dramatic development when a terrifying disease struck monkeys imported from the Philippines to the United States for research, while they were in quarantine in Virginia. Symptoms were similar to the clinical picture of Ebola hemorrhagic fever with 100% fatality, but despite extensive contact between caretakers and monkeys, no humans developed any signs of illness and only four handlers even showed antibody evidence of infection. The virus was subsequently found to have originated in captive macaques in the Philippines and was identified as a new Ebola virus, named Ebola Reston.¹¹¹ There have still been no human illnesses attributed to Ebola Reston but in 2008, the Reston virus was identified as the cause of an epidemic of hemorrhagic fever in pigs; again, animal caretakers had antibody evidence of infection but no humans developed

disease.^{112,113} This is important because it suggests that pigs – known to also be infected with EBOV Zaire – could potentially serve as the site for development of a new recombinant virus capable of infecting humans with an extremely high fatality disease.

In November 1994 after 15 years of epidemiologic silence, Ebola virus (EBOV) re-emerged in Côte d'Ivoire, West Africa. During an outbreak of fatal viral hemorrhagic fever among western chimpanzees in the Taï National Park, a new EBOV subtype was isolated when a scientist performing necropsies on the infected chimps developed symptoms of Ebola virus disease and a new subtype was isolated from her blood. The virus was called Ebola Cote d'Ivoire.¹¹⁴ In 2010, the virus was renamed Ebola Tai Forest in honor of the rainforest where the virus was detected. There has never been another identified case of human disease related to infection with Ebola Tai Forest.

The next epidemic was not until 1995 in the Democratic Republic of Congo (DRC, once Zaire), but between that outbreak and 2014, 24 additional localized outbreaks of Ebola hemorrhagic fever (EVD) occurred in seven African countries including the DRC, Sudan, Gabon, Cote d'Ivoire, South Africa, and Uganda. Major outbreaks occurred in the Congo in 1995 (EBOV Zaire; 315 cases, mortality rate 81%), Uganda in 2000 (EBOV Sudan; 425 cases, 53% mortality rate), and the Congo in 2002 and 2005 (EBOV Zaire; 143 and 264 cases; mortality rates, 89% and 71%).¹¹⁵

After a major outbreak of Ebola Zaire disease in the DRC in 2007, there were numerous reports of a mysterious illness in the Bundibugyo District of western Uganda at the end of the year. A novel EBOV virus species was identified in diagnostic samples submitted to the Centers for Disease Control and Prevention. This fifth Ebola subtype was called *Bundibugyo ebolavirus* (BEBOV) and in response to its detection, an international outbreak response found a large number of the confirmed patients reported having had direct contact with a single person who died of a severe hemorrhagic febrile illness consistent with EVD in November 2007. Bleeding from any site was reported in 54% of patients with a confirmed diagnosis. As with all previous large EBOV outbreaks, there was a temporal lag of approximately 3 months between the initial cases and the identification of Ebola virus as the cause of the outbreak, allowing for prolonged person-to-person transmission of the virus. Ultimately, there were 131 identified cases with a mortality rate of 32%.^{116,117}

During this period of increasingly frequent Ebola virus outbreaks, the search for the source of the virus continued. Between 2002 and 2004, there were five human EBOV Zaire outbreaks in western central Africa, in Gabon and the DRC. Each human outbreak was accompanied by reports of gorilla and chimpanzee carcasses in neighboring forests.¹¹⁸ In each outbreak, scientists found that the first human case had developed the illness after handling a distinct animal carcass: gorilla, chimpanzee or duiker (a small antelope that is known to eat carrion). The animal carcasses were located using global positioning satellite

technology and evaluated by a combination of techniques. In total, the carcasses of 10 gorillas, three chimpanzees, and one duiker were confirmed to be infected by EBOV. Nucleotide sequencing of samples from all infected humans showed variation between epidemics but none between samples from the same outbreak, with eight EBOV Zaire strains identified in the five human outbreaks. In one case, serum from the index case for a human epidemic was positive for EBOV-specific IgG and EBOV virus sequences matched those detected in the bone marrow of the gorilla identified as the source of the outbreak. Nucleotide sequence variations distinct from those previously seen in humans were identified and matched those found in infected tissue from dead animals. Overall, this evidence suggests that these outbreaks were the result of multiple independent introductions of the Ebola virus into humans from infected great apes.¹¹⁸ Subsequently, significant declines in the gorilla population in central Africa were reported with evaluation suggesting that in 2002 and 2003, EBOV Zaire killed about 5000 gorillas in this area. The lag in mortality onset between neighboring gorilla groups paralleled the Ebola disease cycle length, suggesting that group-to-group transmission had amplified gorilla die-offs.¹¹⁹

However, great apes and duikers cannot be the reservoir host for the Ebola virus because they are clearly highly susceptible to EBOV infection and disease. Bats were long suspected to be the natural reservoir for the Ebola virus and in 2005, evidence of asymptomatic EBOV infection was detected in three species of fruit bat during evaluation of more than a thousand small vertebrates collected during Ebola outbreaks in humans and great apes between 2001 and 2003 in Gabon and the Republic of the Congo. Antibodies and nucleotide sequences specific for EBOV Zaire were detected in the liver and spleen of three fruit bat species in Gabon and the DRC (*Hypsignathus monstrosus*, *Epomops franqueti* and *Myonycteris torquata*). This finding has led to the working hypothesis that bats are the reservoir for this deadly virus with gorillas, chimpanzees, and duikers as intermediate hosts.^{120,121}

In early outbreaks, the acute onset of the disease in isolated rainforest settings remote from medical and scientific facilities made acquisition of knowledge about the virus and the disease difficult. Over time, much has been learned: Ebola is contagious – i.e., it is transmittable from one infected individual or animal to another. The first human case in an outbreak of Ebola is usually acquired when blood, secretions, or other body fluids of an infected animal enter a healthy person's body through the mucous membranes in the eyes, nose or mouth, or through an often very small break in the skin. This is most often associated with butchering an infected animal for food, but can occur after handling an infected animal, eating food that infected animals have drooled or defecated on, or by touching surfaces covered in infected droppings and then touching the eyes, nose or mouth. Subsequent spread is direct, from person to person and the secondary transmission rate is low, averaging 1–4%. Surveys of surviving household members have shown that transmission requires extensive direct physical contact with an infected person in every case, especially with exposure to body fluids.¹²² Those who touched the body of someone who had died, especially if this involved traditional preparation for burial, and those who

were exposed during the late phase of the illness were at highest risk.¹²³ People can also become infected through contact with objects, such as needles or soiled clothing, contaminated with infected secretions (aka fomites). Healthcare workers – at risk for infection by both of these methods – have frequently been infected in Ebola outbreaks, with as many as half of some outbreak populations consisting of healthcare providers.¹²³ Once the virus makes direct contact with the blood or mucous membranes, it is highly infectious: an infinitesimally small amount of virus in direct contact with blood or mucous membranes can cause illness. Experiments on nonhuman primates suggest that even a single virus may be enough to trigger a fatal infection. Ebola virus is considered to be only moderately contagious because it is not spread through routine, social contact (such as shaking hands or sitting next to someone) and there is no evidence of transmission through intact skin or airborne spread through droplets with coughing or sneezing.¹²⁴

The incubation period of Ebola virus disease (EVD) – previously known as Ebola hemorrhagic fever – ranges from 2 to 21 days but symptoms most commonly begin 8–10 days after contact with the virus. Illness onset is sudden, with fever, headache, joint and muscle pain, sore throat, and intense weakness. This is followed by stomach pain, diarrhea, vomiting, rash, and impaired kidney and liver function. Many patients develop red eyes due to conjunctival injection, hiccups and signs of internal and external bleeding. In 50–90% of cases, severe hemorrhage, multiple organ failure and shock develop, resulting in death. Survivors were previously not thought to be infectious but the virus persists in semen for up to 3 months post recovery and sexual transmission has been confirmed.¹²⁵

The path from EBOV infection to clinical disease involves primarily a dramatically exaggerated immune response. Dendritic cells and macrophages, sentinels of the innate immune response, are involved early in the response to invasion. Activated dendritic cells carry the virus from the initial site of infection to lymph nodes, the spleen and the liver where intense replication takes place. Viral proteins inhibit immune responses, allowing relentless viral replication throughout the body. Extensive infection of monocytes and macrophages – the body's white cells that fight infection – leads to dramatic over-release of inflammatory and pro-inflammatory cytokines and chemokines, and this massive inflammatory response – similar to the cytokine storm seen with severe influenza – can result in impaired endothelial cell function and significant vascular leakage. There is massive cell death of T lymphocytes, eliminating a significant component of the adaptive immune response. In the worst cases, multifocal necrosis of hepatocytes (liver cells) leads to progressive liver failure; destruction of secondary lymphoid organs and other tissue damage results from direct cytopathic effects but also from the host response. Together, these events can lead to multi-organ failure, impairment of the vascular system, terminal shock, and death.^{126,127}

The characteristic hemorrhage seen with end-stage Ebola is the result of disseminated intravascular coagulation (DIC), a process in which the body's clotting system is inappropriately activated in response to specific triggers. With Ebola virus infection, the trigger appears to be release of a transmembrane glycoprotein called

tissue factor which is expressed by infected macrophages in response to inflammatory cytokines and vascular damage. Tissue factor initiates the clotting cascade and in response, small fibrin clots form in blood vessels all over the body. The clots can impede flow to vital organs, especially the liver, brain, and kidneys, leading to progressive organ damage. Because clotting factors are used up in the process of producing these clots, they are not available to prevent bleeding, leading to internal and external hemorrhage wherever vascular integrity is compromised. Even when overt bleeding does not occur, clotting times are prolonged and fibrin split products are often detected.^{126,127}

Viral levels are dramatically higher from the beginning of the illness in patients who go on to die. High viral levels persist for up to 7 days after death, explaining the high risk of infection associated with preparing bodies for burial.^{128,129} It is the combination of direct viral effects and the excessive host response which drives the devastating pathophysiology of Ebola virus infection.

The Virus

Ebolaviruses are members of the family Filoviridae, which also includes the severe human pathogen Marburg virus (genus *Marburgvirus*) and the Lloviu virus (*Lloviu cuevavirus*; genus *Cuevavirus*). The Filoviridae family belongs to the order Mononegavirales, a group of viruses characterized by a linear, non-segmented, single-stranded negative RNA genome.¹³⁰ The morphology of the Ebola virus is unique among viruses: by electron microscopy, the virus appears as long filamentous strands about 14,000-nm long and 80-nm wide. The strands contain a tubular nucleocapsid with surface spikes and on electron microscopy, they assume characteristic shapes including a shepherd's crook and the number six as shown in Figure 7.1. The Ebola virus is a negative-sense single-strand RNA virus with a 19 kilobase genome, and like most other RNA viruses quickly generates mutations through error-prone replication. The RNA genome of the Ebola virus encodes seven viral proteins including a nucleoprotein, a glycoprotein, and a polymerase.¹³⁰

There are five identified EBOV subtypes – Zaire, Sudan, Tai Forest, Bundibugyo, and Reston – each named for the site where they were first identified. The Reston virus does not cause disease in humans. Significant outbreaks have been caused primarily by Ebola Zaire (also known as ZEBOV) and Ebola Sudan (SEBOV). Nucleotide sequencing has shown significant variation in viral strains between epidemics but little or no variation between isolates from the same outbreak.¹³¹

Over the past 30 years, three basic methods for detecting infection and/or disease with Ebola virus have been developed for use in clinical laboratory settings: serologic tests that detect host antibodies generated against the virus; antigen tests that detect viral proteins; and molecular tests that detect viral RNA sequences. In the early years, serologic tests were used to confirm the cause of disease outbreaks because antiviral antibodies persist for years following infection. However, the variable onset of antibody responses during acute illness makes serology much less useful in the acute setting. Antigen detection and molecular tests

are very effective for acute diagnosis as virus levels in the blood typically rise to high levels as soon as symptoms begin. No tests reliably detect Ebola virus prior to the onset of symptoms.

Accurate diagnosis of Ebola virus infection is a critical part of an effective outbreak response, but establishing safe, rapid diagnostic testing in resource-poor environments has been challenging. Ultimately, RT-PCR testing has become the standard for Ebola virus diagnosis. With RT-PCR, RNA molecules are converted into their complementary DNA sequences (cDNA) using reverse transcriptase enzymes, followed by amplification of the newly synthesized cDNA by standard PCR procedures. There are several standard, real-time RT-PCR tests approved for emergency use by the WHO and FDA, and four of these are commercially available as kits. Real-time RT-PCR diagnosis in an outbreak setting still requires field labs with substantial infrastructure and staff with expertise in molecular techniques.¹²⁸

There has been no specific treatment for EVD although experimental antiviral medications are being tested now. Outbreaks are managed by isolation of infected individuals, quarantine of contacts and barrier protection of healthcare workers. In the small, unsophisticated communities in which EVD typically develops, this requires active surveillance using several methods, including house-to-house search, review of hospital and dispensary records, interview of healthcare personnel, retrospective contact tracing, and direct follow-up of suspected cases, all carried out with sensitivity and tact. It is easy to appreciate how difficult this is to accomplish when outbreak management is attempted by teams of masked white foreigners in full-body protective suits descending upon frightened members of isolated African communities. In the usual situation, access to medical or scientific support is limited. Specific education to allow rapid identification and isolation of new cases and to halt the highly infectious traditional burial methods has been critical in arresting disease spread – again, this requires cooperation and trust between the community members and the outbreak support team.¹³²

To avoid transmission of Ebola virus to care providers in hospital settings, great care needs to be taken to avoid contact with infected bodily fluids. This has proven very difficult to accomplish. Patients must be isolated, and strict barrier nursing techniques used, including masks, hoods with eye screens, double gloves, impermeable gowns and boots. Invasive procedures such as the placement of intravenous lines, handling of blood, secretions, catheters and suction devices are a particular risk and strict infection control is essential. Other control measures include proper use, disinfection, and disposal of instruments and equipment used in caring for patients. The bodies of those that have died of Ebola virus infection remain highly infectious and must be promptly and safely buried or cremated.

In selected cases, infected Westerners and healthcare workers have been given antiviral agents like ZMapp, a combination of three antiviral antibodies, and plasma transfusions from individuals who had recovered from Ebola and both measures seemed to possibly improve outcomes if given early in the course of the illness. There is ongoing investigation of several different therapeutic strategies that target specific

viral structures and mechanisms of Ebola viruses, some of which have demonstrated promising results in animal studies. These include agents composed of interfering RNAs targeting specific proteins of Ebola viruses, hyperimmune globulin isolated from Ebola animal models, monoclonal antibodies, and morpholino oligomers, small molecules used to block viral gene expression. Limited reports indicate that simple provision of intravenous fluids and oxygen significantly improves patient outcomes.¹³³ The goals of therapeutic agents include prevention of disease development after exposure and moderation of EVD severity and duration.¹³⁴

2014: And Then, Out of Nowhere ...

To this point, the Ebola virus had a well-established reputation as a guerilla pathogen in central Africa, emerging suddenly at random intervals in remote areas, infecting all with extensive contact and causing severe disease which progressed rapidly to death within a few days in more than half of those infected, before disappearing almost as suddenly when no new victims remained. The mortality rate was formidable, but in all the recorded epidemics between 1976 and 2013, there had been only a combined total of 2361 cases and in every outbreak, the disease burned itself out or was arrested by standard isolation techniques.

Then in December 2013, a 2-year-old boy became suddenly and severely ill with fever, diarrhea, and black stools (a sign of GI hemorrhage) in Meliandou, a small village in Guinea, West Africa. He died 2 days later followed by his grandmother, mother, and sister. Because diarrhea was a prominent symptom, and because EVD had never occurred previously in West Africa, Ebola was not initially suspected as the cause, even as illness spread through the village. Some villagers sought help from a traditional healer in the next community and from there, the disease spread rapidly from one village to another without formal recognition as an Ebola outbreak for several months.¹³⁵ By March 2014, almost 4 months later, cases of this severe illness were reported in neighboring Liberia and Sierra Leone, in people who had travelled from Guinea. The international medical aid group MSF sent the first samples for confirmation of what turned out to be Ebola Zaire to laboratories in Hamburg and Lyon at that time. On May 25, scientists confirmed the first case of EVD in Sierra Leone. Epidemiologic investigation discovered a link between this case and the burial of a traditional healer who had treated EVD patients from Guinea. Traditional burial involves preparation of the body by mourners and is associated with extremely high risk of infection. In this specific situation, there were 13 additional cases of Ebola, all women who attended the burial.

By this time, international aid was being provided by teams from the WHO, MSF and the CDC and initially, this appeared to curtail the outbreak in March and April 2014.^{136,137} However, movement of untracked contacts across borders led to continued, uncontrolled spread and by June 2014, the situation had evolved into a public health crisis as the first documented multi-country Ebola epidemic. Ongoing transmission occurred in multiple districts in Guinea, Liberia, and Sierra Leone, including densely populated urban areas in these countries. Most previous Ebola

outbreaks had occurred in remote areas in central Africa so chains of transmission were easier to track and break – familiarity with EVD and how it presents meant earlier recognition and therefore earlier implementation of isolation techniques. The current outbreak was different with large villages and urban areas as well as remote rural areas affected, vastly increasing opportunities for undiagnosed cases to interact with others and further spread the disease.

Intense fear ruled all three countries and mistrust of healthcare teams was prominent. As the outbreak progressed, overt community resistance began to emerge. Through June and July, containment efforts were increasingly hindered by local resistance and hostility toward doctors, flight of persons suspected to have the disease, involvement of multiple locations, and the cross-border movement of infected individuals. In some communities, aid workers were physically threatened, and barriers were erected across roads preventing workers from reaching villages with suspected cases. Travel warnings for symptomatic persons leaving affected parts of Africa went unheeded. Case numbers from all three countries continued to increase and cases appeared in other parts of Africa where patients had traveled.

On August 8, 2014, the WHO officially declared the outbreak to be a Public Health Emergency of International Concern.¹³⁷ By this time, there had been 2000 known cases and more than half had died. Then in August, two American missionaries working with an international medical aid group were infected.¹³⁸ Their emergency evacuation to the United States suddenly brought widespread international attention and then panic as health officials and the general public realized that this disease with its incredibly high mortality rate had the potential to spread around the world. By this time, more than 240 healthcare workers had developed EVD in Guinea, Liberia, Nigeria, and Sierra Leone, and more than half of these individuals had died.¹³⁹ Shortages of personal protective equipment or its improper use, limited medical staff for large numbers of patients, and the compassion that caused medical staff to work in isolation wards far beyond the recommended number of hours all contributed to the high rate of medical staff infection. In the early months of the epidemic, not even gloves or masks were available in some settings. Existing healthcare infrastructure was minimal – WHO estimates that, in these three hardest-hit countries, only 1–2 doctors were available to treat 100,000 people, and these doctors were heavily concentrated in urban areas. Before the outbreak, health indicators in West Africa were among the worst in the world, particularly in terms of maternal and child health. In this fragile context, the outbreak completely overwhelmed the existing health systems and this contributed to fear and mistrust of exhausted healthcare workers, closure of health facilities, and the deaths of health service staff.¹³⁹

September 2014 – when I first became aware of the pandemic – saw the beginning of an international governmental response with the first official commitment from the US of 500 million dollars and 3000 troops deployed to the area to deliver supplies and build new treatment centers. Many other countries including China, France, the United Kingdom, Canada, and Cuba sent nurses, doctors, infectious disease specialists, supplies, and other forms of aid to augment existing relief efforts

in West Africa. At that time, the United Nations described the severity of the outbreak as unparalleled. On September 30, 2014, an American who had traveled to the US from Liberia was belatedly admitted to a Dallas hospital with a diagnosis of Ebola – he was the first case of Ebola diagnosed in the United States. Despite maximal care, albeit late in the course of the disease, this patient died and two of the nurses who cared for him were infected. Although they both survived, these cases created a public health crisis in the United States with widespread panic fueled by 24-hour media coverage.¹⁴⁰

Through the fall of 2014, the epidemic continued to grow. Multiple healthcare workers were emergently transported back to their home countries with Ebola. On the ground in West Africa, medical teams struggled in protective gear that was so hot and confining they could only work 4-hour shifts – one nurse described literally pouring sweat out of her rubber boots at the end of her shift because it was so hot in her hazmat suit. Attempts were made by teams of international workers to identify and isolate all potential cases despite continuing bed and facility inadequacies. A new WHO report found that health workers were between 21 and 32 times more likely to be infected with Ebola than people in the general population – needless to say, this affected recruitment of additional medical personnel.¹⁴¹

In early October, the UK announced that it would introduce temperature screening for passengers arriving at Gatwick and Heathrow airports from West Africa followed by a similar statement regarding JFK airport in the United States. On October 14, the WHO announced that the fatality rate from Ebola had reached 70%, with the total number of known cases at 6353 and deaths at 4447. Global panic was at its height.

On the ground, efforts at public education gradually led to earlier identification of cases and cessation of the traditional burial techniques. Isolation of cases and quarantine of identified contacts gradually slowed the number of new cases with both Liberia and Sierra Leone reporting the lowest numbers in 6 months during the first week of January 2015. By May 2015, Liberia was reportedly Ebola-free with continually declining cases in Sierra Leone and Guinea. On May 9, 2015, WHO declared the end of the Ebola outbreak in Liberia and on November 7, 2015, WHO declared Sierra Leone free of Ebola virus transmission. On December 29, 2015, the WHO declared Guinea free of Ebola virus transmission. In total, there were over 28,000 cases with more than 11,300 deaths in the 2014–2015 Ebola pandemic.^{140,141} Figure 7.2 shows the number of cases reported to the WHO per week by country from March 23, 2014 to January 3, 2016.¹⁴²

Global Pandemic Averted

The Ebola virus was introduced into Nigeria on July 20, 2014 when an infected Liberian man arrived by air in Lagos, Africa's largest city with 21 million residents.¹⁴³ Lagos is an international travel hub with departures via every conceivable mode of transportation to cities throughout Africa and the world: spread of Ebola in Nigeria could have quickly turned a regional epidemic into a global catastrophe.

Weekly reported Ebola cases

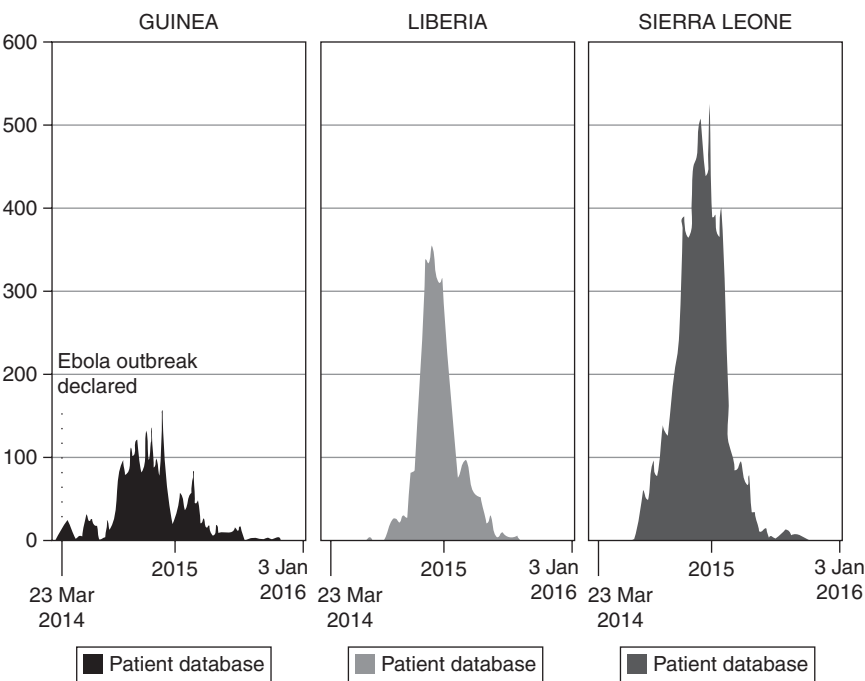


FIGURE 7.2 Ebola cases reported to the WHO from Guinea, Liberia, and Sierra Leone by week, from March 23, 2014 to January 3, 2016.

At the airport and in the hospital where he was admitted, the traveler came into direct contact with 72 people before he was diagnosed with Ebola. He infected 13 of these initial contacts with the virus, one of whom fled quarantine to travel by air to Port Harcourt, Nigeria's oil capital, further spreading the infection to doctors and others in that city. It looked as though a nightmare scenario – the exponential spread of Ebola in multiple urban centers – could become a reality.¹⁴³

All the elements for a global epidemic were in place but prompt action by local and international public health teams prevented this from occurring. Unlike the three nations in West Africa where the Ebola epidemic was raging, Nigeria has a functioning public health infrastructure including an emergency operations center and incident management system established previously by the CDC and international partners as part of the global effort to eradicate polio. When the Ebola virus landed in Nigeria, the government had the critical systems already in place to detect people potentially infected with the virus and interrupt transmission before it could spread out of control. Nigeria also had a team of epidemiologic disease detectives trained through the CDC's Field Epidemiology Training Program (FETP). Within hours after the initial patient's positive Ebola diagnosis, Nigeria's FETP trainees spread out across Lagos, looking for anyone who might have come in contact with

the traveler – the process of contact tracing. CDC staff in Nigeria and from Atlanta became part of the incident management system providing a coordinated, urgent response. The teams identified 894 people at risk for Ebola and completed nearly 19,000 home visits to monitor these individuals for symptoms over the 21-day incubation period post exposure.

At the airports, more than 147,000 travelers were screened for fever that might indicate Ebola infection. Eventually, these efforts identified 19 additional people with Ebola across three generations of transmission in the two cities and ended the outbreak before it could spread further among Nigeria's population of about 180 million people, or beyond. The immediate, rapid response made possible by the existing infrastructure and trained epidemiologists in Nigeria is a model for how potential global pandemics can be contained and controlled.¹⁴³

Identifying the Outbreak Source

The severe West African Ebola epidemic is thought to have stemmed from EVD in the 2-year-old index case in Meliandou, Guinea. Researchers explored the source of that original infection using wildlife surveys, interviews, and molecular analyses of bat and environmental samples, and showed that there had been no decline in larger wildlife like apes, gorillas, and duikers in the Meliandou area before onset of the epidemic. Interviews with regional authorities, hunters, and women of the village revealed that primates are rare and difficult to hunt in south-eastern Guinea. Most large game consumed in the region arrives smoked from distant regions, eliminating it as a source of the infection. If contaminated fresh bushmeat had been brought to the village by a hunter, the latter would likely be among the first cases, as observed in previous outbreaks in the Congo Basin. Instead, only children and women developed symptoms and died in the beginning of the 2013–2015 epidemic. Collectively, these findings suggested that larger wildlife did not serve as an intermediate amplifier leading to the infection of the index case in Guinea, by contrast with the majority of Central African Ebola outbreaks.¹³⁵

As previously reported, bats are considered to be the natural reservoir of the Ebola virus. Children in Meliandou were known to regularly catch and play with small insect-eating bats in a large hollow tree very near the home of the index case. Researchers speculate that this 2-year-old child may have been infected by playing near that tree which reportedly housed a very large colony of insectivorous free-tailed bats (*Mops condylurus*). Bats in this family are considered potential sources for Ebola virus outbreaks, and experimental data have shown that this species can survive experimental infection.¹⁴⁴ Molecular analyses of bat and environmental samples identified 13 different bat species. Three of the species captured – *Eidolon helvum*, *Hypsignathus monstrosus*, and *Mops condylurus* – were previously reported as possible reservoirs for Ebola virus, but no EBOV RNA was detected in any of the PCR-tested bat or environmental samples from Meliandou or the surrounding area. Attempts to demonstrate the presence of IgG antibodies against Ebola viruses were also inconclusive. The investigation suggested but did not prove that unlike the

majority of previous outbreaks, infection of the index case in this epidemic most likely involved direct infection from a bat reservoir.¹³⁵

Looking Back :: Moving Forward

This Ebola pandemic was unique: it was by far the largest Ebolavirus outbreak in history with more cases, survivors, and deaths than all other outbreaks combined. It included cases in 10 countries with limited international spread and lasted for almost two and a half years. What happened? Analysis of the outbreak has identified many critical factors, most important of which is delayed recognition of the cause of the disease as Ebola – EVD had never occurred previously in West Africa so awareness of its typical presentation was minimal. Formal disease surveillance systems, a critical factor in recognition and arrest of disease outbreaks, are limited in the affected West African countries. Once Ebola was recognized – a long 3 months after the index case – public health education campaigns were slow to begin and not optimally delivered: the primary countries affected by Ebola have some of the world's lowest literacy rates so messages and delivery needed to be tailored to address this. Health resources were already constrained when Ebola hit: Sierra Leone, Liberia, and Guinea are among the poorest countries in Africa with fragile health systems so capacity to respond to a major health emergency was limited. The international community response was slow with the declaration of a Public Health Emergency of International Concern by the WHO delayed until 5 months after the epidemic was recognized and 8 months after it began; there is little doubt that the status of WHO has suffered in response to their handling of this epidemic. Finally, the outbreak emphasized the important role of increasing global interconnectedness associated with the acceleration of international travel and trade allowing greater opportunities for infectious diseases like Ebola to emerge and spread.^{136,145–147}

This devastating Ebola pandemic led to immediate efforts to develop a vaccine to prevent and/or limit future outbreaks. A collaborative global effort coordinated by the WHO resulted in accelerated development of candidate vaccines funded by the US National Institutes of Health, the Wellcome Trust, the European Commission, the UK Medical Research Council and the Bill & Melinda Gates Foundation. After the attacks on the USA on September 11, 2001, several governments had invested in Ebola virus vaccine research because of concerns it could be used as a biological weapon.¹⁴⁸ Based on results from these studies, candidate vaccines were rapidly designed, developed and manufactured in the US, Canada, Europe, and Asia with trials initiated in these countries plus Africa and Australia. A total of 10 clinical studies were conducted in support of potential eventual registration of an Ebola vaccine. With a lethal pathogen like Ebola, licensure is approved on the basis of animal studies plus evidence of safety and a proven immune response.¹⁴⁹ Clinical trials used administration of the vaccine to healthy human subjects to evaluate the immune response and identify side effects in accelerated protocols. Viral-vectored vaccine candidates entered Phase I clinical trials including a recombinant replication-competent vesicular stomatitis virus (rVSV) model and a recombinant

chimpanzee adenovirus serotype 3 (ChAd3), both encoding the EBOV glycoprotein. Both vectors were previously shown to be safe in human studies for other candidate vaccines. The rVSV-ZEBOV vaccine was studied in a trial involving 11,841 people in Guinea at the end of the epidemic in 2015. Among the 5837 people who received the vaccine, no Ebola cases were recorded 10 days or more after vaccination. In comparison, there were 23 cases of EVD occurring 10 days or more after vaccination among those who did not receive the vaccine. The rVSV vaccine had no severe safety concerns and was shown to be 100% efficacious and 75% effective at the cluster level, including herd immunity in unvaccinated cluster subjects.^{150,151}

The rVSV vaccine was then chosen to be used on an expanded access basis in March 2016 in response to a recurrent outbreak of EVD in Guinea. An innovative ring vaccination strategy was used based on the technique developed and proven effective during the smallpox eradication campaign. It involved aggressive surveillance for EVD cases and contact tracing with vaccination of all contacts and people at risk. The rVSV trial, called *Ebola ça Suffit!*, showed the vaccine to be highly effective after a single dose when used in this setting. Over a 1-month period, 1510 individuals were vaccinated in four rings including 307 healthcare workers. No secondary cases of EVD developed among those vaccinated and there were no serious adverse events.^{151–153}

The risk of human infection from pathogens like Ebola is ongoing, persistent and – to this point – unpredictable. Evidence from 40 years of previous Ebola outbreaks suggests that the classic disease response approach is effective: early case detection and isolation based on community education and engagement; comprehensive contact tracing and quarantine; supportive clinical care; and rigorous infection control including safe burial methods. To these we can now add the use of vaccine to halt outbreaks as soon as the first cases are identified. However, every effective response depends on early recognition of the first cases of a new disease outbreak, and this requires that existing healthcare inadequacies in countries like Guinea, Sierra Leone, and Liberia be addressed. A robust national health service with an adequate healthcare infrastructure, an existing disease surveillance system, and ongoing community health education programs are the minimum requirements for disease detection, the critical steps in controlling any potential epidemic infection. As the transport of Ebola to Nigeria showed, an existing public health system can swing into action and very effectively prevent disease spread.¹⁴³ Immediate development of national health services linked to continental and international programs is the critical first step in preserving the future of global health security. Achieving this transformation of health systems on a global basis will require sweeping reforms led by a re-invigorated and reorganized WHO backed by an enormous commitment of financial and human resources.^{154,155}

On a more focused level, development of effective treatment methods is a very high priority. In September 2014, the World Health Organization launched a fast-track process to identify potential anti-Ebola drugs with four potential classes of products: immunomodulators, immunoglobulins, small inhibitory RNA, and

antivirals.¹⁵⁴ Three criteria were established for a drug to be acceptable as a candidate for clinical trials: available safety data in humans, evidence for in-vivo efficacy against Ebola virus from preclinical studies, and sufficient drug supply.¹⁵⁵ Five potential drugs were identified: Favipiravir, an RNA polymerase inhibitor, originally developed and approved in Japan for the treatment of severe influenza; mAb114, a chimeric monoclonal antibody cocktail; Remdesivir, a novel nucleotide analog prodrug developed for treatment of filovirus infections that blocks replication; REGN3470-3471-3479, a co-formulated cocktail of three human monoclonal antibodies targeting the EBOV glycoprotein; and ZMapp, a triple monoclonal antibody cocktail, already tried in selected cases during the 2014–2015 epidemic that targets three Ebola glycoprotein epitopes.

The WHO concluded that large and complex trials, in which treatments are randomized to a selected, homogeneous group of individuals – the usual standard for drug trials in a first world setting – are impractical in the field, given the typically fragile healthcare systems in countries with ongoing Ebola outbreaks. With the large number of patients presenting simultaneously, the very high mortality rate of the disease and the impossibility of explaining a randomization process to very sick patients, it was concluded that it is both ethically unacceptable and impractical to allocate patients from within the same family or village to receive or not receive an experimental drug.^{154,155} The WHO therefore approved all five available experimental treatments for use at Ebola treatment centers using standardized protocols with each treatment chosen by clinicians on a case-by-case basis. The treatments can be used as long as informed consent is obtained from patients and protocols are followed, with close monitoring, standardized reporting of results and documentation of adverse events.

Update

There have already been four new EVD outbreaks since the onset of the West African epidemic, all in the DRC. The first occurred between August and November of 2014 in the vicinity of Boende town in Equateur province, a dense rainforest area. The index case was a pregnant woman who butchered a monkey found dead in the jungle by her husband – the classic story for initiation of an Ebola outbreak. She developed symptoms on July 26 and died on August 7. After her death, a local doctor assisted by three health workers performed a postmortem cesarean section to separate the fetus from the mother before burial, per local custom. These four individuals all developed EVD and all died. Subsequently, eight symptomatic individuals with suspected EVD were evaluated and cultured at the local health center for the province. All cultures were positive for Ebola Zaire; subsequent genomic sequencing revealed the virus was identical or closely related to the EBOV variant that caused the EVD outbreak in the DRC in 1995; it was unrelated to the variant associated with the epidemic in West Africa. Ultimately, there were 66 confirmed patients with most cases presenting in late August and early September. All cases and contacts were found to have arisen from contact with the index case. There were

eight infected healthcare workers and all died. Overall, the mortality rate was 74%. This outbreak, similar to many previous outbreaks in Central Africa, burned out on its own and was declared over on November 14, 2014.¹⁵⁶

On May 11, 2017, the WHO was notified that Ebolavirus Zaire had again been detected among a cluster of undiagnosed illnesses and deaths with hemorrhagic signs in Likati, a remote region of the DRC. Cases of the disease were reported in four health districts. This was DRC's eighth outbreak of EVD since the discovery of the virus in the country in 1976. An effective response to this latest EVD outbreak in Africa was achieved through the rapid identification of cases, immediate testing of blood samples due to strengthened national laboratory capacity, early announcement of the outbreak by the government, and rapid response activities by local and national health authorities with the support of international partners. Medical support by MSF and coordination support on the ground by the WHO Health Emergencies Program were critical; an Incident Management System with deployment of 50 experts was set up within 24 hours of the outbreak being announced. When the new EVD outbreak was announced in May 2017, the rVSV vaccine was approved again for use but this did not prove necessary given the small size of the outbreak and the rapid control achieved.¹⁵⁷ The outbreak was officially declared over by the WHO on June 2, 2017, 42 days – or two complete infection cycles – after the last case. There were eight identified cases with four deaths.¹⁵⁸ In April 2019, a team of local epidemiologists, the WHO and MSF reported complete sequencing of the virus responsible for this outbreak, a novel variant of ZEBOV, genetically close to the Ebola virus Mayinga variant which was identified as the cause of one of the two original 1976 outbreaks in the DRC.¹⁵⁹

On May 8, 2018, local health officials reported a new outbreak with 21 patients showing signs of hemorrhagic fever and 17 deaths in Bikora, in the north-west part of the country, beginning in late April. Three days later, Ebola Zaire was confirmed by RT-PCR testing and the WHO put the DRC and all its neighbors on high alert. Despite aggressive efforts at containment, EVD spread to Mbandaka, a major city in the DRC with a population of more than a million people. At that time, there had been 44 confirmed cases and 23 deaths. WHO officials were very concerned about a major urban outbreak because the Mbandaka cases were the first sign of urban spread in the DRC. They were also concerned about the spread of Ebola in Congo-Brazzaville and the Central African Republic, because they are both connected to the outbreak area through river systems. WHO and Doctors Without Borders initiated emergency vaccination based on contact tracing and by the end of June, 3330 people had received the rVSV vaccine. New cases began to decrease and on July 24, 2018, the health ministry declared the outbreak over. The authorities recorded 53 confirmed and possible cases of Ebola starting in April, 29 of which were fatal.

Only a week later on August 1, 2018, a new Ebola outbreak in DRC was reported in North Kivu Province in the easternmost part of the country; analysis of genetic sequencing showed that while the outbreak was new, in an area remote

from Bikora, it was the same EBOV Zaire strain that caused the new outbreak, thousands of miles away.¹⁶⁰ Unfortunately, this outbreak was complicated from the outset by ongoing conflict with multiple armed groups in North Kivu Province, which shares a border with Uganda and Rwanda. For decades, eastern Congo has suffered from on-and-off war and it remains beset by ongoing conflicts over land and ethnicity. Since late 2014, approximately 1000 civilians have been killed by both local and state forces in the area around the city of Beni, where a number of health workers were currently based. Health workers in the region were currently relying on the support of the United Nations peacekeeping force to allow them to work. The volatile security situation had the potential to impact the method of vaccination used by WHO to try and contain this epidemic – as with the previous outbreak, health workers were planning to use the ring vaccination method, which targets only those who have potentially been in contact with an infected individual. As of July 2019, more than 1700 people had been vaccinated using contact tracing. If security constraints made screening to identify and vaccinate contacts impossible, all available residents of any village where an EVD patient had been identified were vaccinated.¹⁶⁰ Sustained violence complicated all efforts at care delivery.¹⁶¹

Meanwhile, Congolese health officials began an experimental treatment trial in EVD patients in November 2018 with the monoclonal antibody cocktail mAb114, the antiviral Remdesivir, REGN3470-3471-3479 and ZMapp, all of which are infused intravenously. The four treatments were tested in units run by three medical charities: Doctors Without Borders, Alima, and the International Medical Corps. Patients were assigned at random to get one of the four treatments as part of the PALM trial, for Pamoja Tulinde Maisha, which means “Save Lives Together” in Swahili.¹⁶² In August 2019, the trial’s co-sponsors at the WHO and the National Institutes of Health announced that two of the experimental treatments, now known as Regeneron and mAb-114, dramatically boosted survival rates: among patients with low viral loads suggesting they had been infected only days before, only 6% of those who received Regeneron and only 11% of those who got the mAb-114 drug died. By contrast, 33% of those who received Remdesivir and 24% of those who got ZMapp died and these two drugs were no longer used.¹⁶³ This clinical trial was carried out in the worst possible conditions, but still, dramatic and important results were achieved. With this announcement, a new trial was initiated, directly comparing Regeneron to mAb114. News of an effective cure had the potential to change the course of this outbreak, the worst the Congo has endured.

However, almost 20 months after this epidemic began, the outbreak is still ongoing. Despite intensive international efforts including sustained attempts at contact identification and ring vaccination, despite discovery of effective treatment, conflict in the area has continuously complicated efforts to treat infected patients and to identify contacts, with response teams facing daily challenges against a backdrop of sporadic violence from armed groups and mistrust in affected communities. On July 17, 2019, the WHO had declared the Ebola outbreak in the Democratic

Republic of the Congo to be a Public Health Emergency of International Concern when cases were reported in neighboring Uganda. Cases peaked in the summer of 2019 but despite sustained international efforts, the epidemic still dwindles forward. At the time of this writing in February 2020, there have been more than 3444 confirmed cases, including more than 2264 deaths. Almost one in three “cases” has been a child and 5% of deaths have been among healthcare workers.¹⁶⁴

This last outbreak in an almost continuous series of outbreaks confirms that EBOV is an ongoing presence in the DRC. The incidence of EBOV outbreaks is escalating with three in the last 18 months, a striking difference from the long period of epidemiologic silence that occurred after the first two outbreaks in 1976. Important new risk factors combine to make the DRC particularly vulnerable to epidemic disease spread. Over the last 60 years, there has been exponential population growth – from ~15 million in 1960 to more than 84 million in 2018. This population increase means people are living closer together and to jungle areas and the animals who inhabit them, both factors that facilitate disease spread. Since the 1960s, the Congolese have endured over four decades of armed conflict with an ongoing civil war between government troops and rebel groups in Eastern Congo where the current outbreak began. The sustained levels of violence and conflict have caused massive infrastructural damage, population displacement and loss of life. Although the DRC is one of the richest countries on the planet with an estimated 24 trillion dollars of natural resources, it has one of the highest levels of poverty in the world, ranking first among the 11 poorest countries in 2014: 63% of citizens live below the poverty line. In the past four decades, the political and economic collapse of the country has had a dramatic impact on the country’s healthcare system. Hospitals and clinics lack personnel and equipment, medication and supplies. An estimated 70% of Congolese have little or no access to health care. Even basic infrastructure is deficient: in the DRC, only 1.8% of existing roads are tarred and less than 10% of the population has access to electricity. In terms of factors for epidemic susceptibility – high population density, urban overcrowding, war, poverty, and deficient healthcare infrastructure – the DRC has it all. Major efforts by international groups to address deficient healthcare infrastructure are ongoing but all the factors necessary for a disastrous pandemic persist.

But now the picture has changed. For the last 40 years, the specter of the Ebola virus has hung over Africa and haunted scientists, infectious disease specialists, and public health experts all over the world. Until now, many believed that anyone infected with Ebola in the current era was “doomed to die alone among space-suited strangers and be buried without ceremony in a bleach-misted body bag.”¹⁶⁵ Major scientific advances achieved on the ground in the last 5 years during the West African epidemic and the current outbreak in the eastern DRC have resulted in an effective vaccine and two powerful antiviral treatments. As of February 20, 2020, the DRC, Burundi, Ghana, and Zambia have licensed an Ebola vaccine, just 90 days after the WHO completed an accelerated pre-qualification process.¹⁶⁶ Licensing means that the manufacturer can stockpile and widely distribute this vaccine to African countries at risk of Ebola virus disease outbreaks. Disease prevention,

deficient healthcare infrastructure and delivery of care to distrustful infected individuals remain ongoing challenges, but for the first time, there is major progress towards turning Ebola from a terrifying, highly fatal disease into one that is preventable and treatable.

Out of Nowhere?

West Nile virus, SARS, Ebola, and Zika are unique viruses, but each led to a completely unanticipated, explosive global pandemic. Did they really come “out of nowhere”? Many of the characteristics associated with pandemics through history are readily identified: specifically, the sudden emergence of a previously unknown disease; and the critical role of travel bringing a new contagion to an immunologically naïve population. Only SARS was truly a previously unidentified pathogen while WNV, Ebola, and Zika were all thought to have been well characterized. For all four viruses, travel was important, introducing a new contagion to a location where the disease was unknown and the population had never previously been exposed. In fact, in today’s highly interconnected world, rapid, frequent global travel played a critical role in the introduction and global spread of each of these viruses, as did our exponentially increasing world population density and chaotic urbanization.

Perhaps most importantly, these pandemics emphasize the importance of the unique characteristics of viral pathogens. WNV was known to be carried by mosquito vectors from avian reservoirs and was recognized in Africa, the Middle East, Eurasia, and Australia for causing sporadic outbreaks of a generally mild disease, but it was not until the virus reached NYC in 1999 that it was definitively shown to cause simultaneous deadly outbreaks in birds and serious neuroinvasive disease in people. That initial epidemic ended when cooler weather eliminated mosquitoes, but astonishingly, the virus spread to infect millions of individuals and involve the entire Western Hemisphere over the next decade. We underestimated the power of spontaneous viral evolution leading to enhanced neurovirulence; and the incredible speed of disease transmission in an enormous, naïve population, replete with available reservoirs and carriers where global warming led to a longer period for disease transmission.

With SARS, a previously unidentified but very highly contagious virus caused a widely transmitted, rapidly progressive, sometimes fatal pneumonia that over a 6-month period affected more than 8000 individuals in 30 countries. Among its important lessons is the lethal capacity of viral pathogens that jump from animals to infect humans. The SARS pandemic emphasized the power of international air travel in contemporary disease transmission – so powerful that the right pathogen can threaten the entire planet. With Ebola, months of delay turned a theoretically containable local outbreak into a massive pandemic, and analysis of the delay identified the importance of high population density and poor existing healthcare infrastructure as major risk factors for infectious disease spread. With both WNV and Zika, we under-estimated the power of a minor virus we thought we knew,

introduced by international air travel to countries replete with the necessary vector and an enormous, immunologically naïve population, and we failed to identify the spontaneous development of enhanced neurovirulence with both viruses and the risk this posed for infected subjects and the developing fetus.

Analysis of these four pandemics does not support the “out of nowhere” concept, but instead highlights important themes in contemporary viral pandemic development: the critical roles of ongoing viral evolution and of emerging viruses that can cross over from other species to infect humans; the very high importance of global travel in disease introduction to new populations; the speed of disease spread in our crowded, increasingly connected world; and the importance of global scientific communication and collaboration. Critical evaluation of an outbreak focused on these characteristics could potentially interrupt disease spread.

There will be another viral pandemic – and the world may again feel that it came “out of nowhere.” But the response to the WNV, SARS, Ebola, and Zika epidemics will hopefully have left us better prepared to use intensive outbreak analysis of the virus itself plus international surveillance systems, continuous global pathogen-specific scientific investigation and communication, and immediate international collaboration to establish effective pandemic disease defenses.

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8

A WAY FORWARD

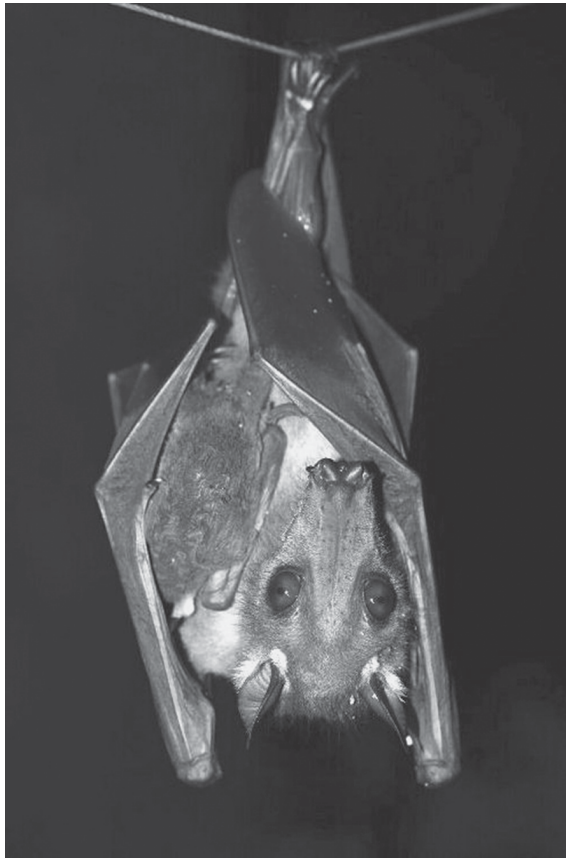


FIGURE 8.1 An adult female hammer-headed fruit bat with attached young in the Republic of Congo. Bats are the natural reservoirs of many viruses including Ebola, SARS, and SARS-CoV-2, the cause of COVID-19.

Source: National Institute of Allergy and Infectious Disease, US National Institutes of Health. niaid.nih.gov

A CAUTIONARY TALE

My brother-in-law Chris is an intrepid international traveler – his last two job postings were in Nepal and China and he lived in Africa for years – but even for him, this trip seemed like a bit of a stretch. In order to include his son and family in this year's Christmas celebration, he was flying from Ottawa to Songdo, South Korea, where Graeme was teaching for just six days, returning on December 19th. The outbound trip was not too bad with flight changes in Toronto and Vancouver, but the return was a killer – almost 20 hours via Beijing, Vancouver, and Toronto before finally reaching home. I admired his commitment, but I was glad I was not going with him!

Like many families, our Christmas celebration has become increasingly complex as our children have become grown-ups with families of their own. Home base is my sister's house in Ottawa, but her two daughters split their time with their dad so the big celebration is just on Christmas Day. My husband and I always arrive on the 23rd and leave for home on Boxing Day. My daughter Allison and her partner have a horse farm and take care of all the chores on the 25th so their employees can have the day off, so we have a separate celebration with them – Noel Deux – over New Year's at our place. Chris' two sons and their families are with us roughly every other Christmas, from their homes in South Korea and outside Halifax, but neither would be there this year; hence, Chris's trip to Songdo. There were a few added complexities – Marisa, the elder of my two nieces, was leaving for Mexico to meet her significant other very early on December 26th. Her younger sister Rebecca was flying to Germany on December 27th with her husband and their two young children to visit her father-in-law. And Allison was setting off for Florida along with a van of horses for the winter dressage competitive season on January 3rd. The modern family in motion ...

One of the joys of my life is the close, easy friendship we have with Sarah and Chris. On Christmas Eve, the four of us ate dinner in front of the fire – Chris and I shared a bowl of cheese fondue opposite Les and Sarah, dipping in chunks of French bread from a big basket. This year for the first time they had an artificial tree – an elegant, contemporary metal structure with colored lights at the end of elongated black limbs. I remember thinking how perfectly it suited the modern, vertical design of their townhome. After dinner, we called Graeme, Rachel, Julius, and Genny in Songdo on Skype – they are 14 hours ahead of us, so the kids already had their gifts to show off. Then we ate dark chocolate and drank red wine while we got the stockings ready for the next day.

It must have been about 4 AM when I heard Sarah calling me. Chris was ill with severe diarrhea that had started at about one in the morning. I shifted into doctor mode – the stools were liquid, dark brown and frequent, almost every 15 minutes – “just pouring out,” reported Sarah. He had cramps but no nausea, vomiting or fever. He had taken one loperamide tablet with no

apparent response. Peering up the stairs to their bedroom, he still looked healthy enough and his voice was strong. With his recent trip in mind, I thought it was probably the infamous “traveler’s diarrhea” and recommended two loperamide tablets now and a glass of water once every hour and/or every time he had a stool.

By 7 AM, things were no better – he thought the stool volume was decreasing but it was still very frequent. Color was still brown (I was ruling out cholera) and cramps were maybe a little better, but he did not feel at all well. We started Gatorade instead of water plus loperamide every 4 hours and tried to be encouraging – supportive clinical care at its minimal best. It was at this point that our focus shifted to prevention – everyone was scheduled to arrive in the late morning and it was imperative that we minimize any risk of spread. Of course, we could have called off the celebration but no-one wanted to do that – it was Christmas after all! We closed the door to the stairs to the master suite – isolating our index case. I felt badly shutting Chris away but it had to be done. We agreed that Sarah would be his only physical contact – she would wear disposable gloves and use disinfectant wipes for cleaning. She laundered the bed linens and pj’s with bleach – I remember multiple trips up and down the stairs to the basement laundry all day long. We stocked all the bathrooms with disinfectant hand wipes and talked with Marisa and Rebecca so they and the kids would be aware of the risk and the infection control plan.

When the children arrived, Rebecca took them through use of the hand wipes and the strict rule that nothing could be eaten without washing their hands very carefully first. We opened our stockings and scrubbed our hands before we started on the oranges and chocolate. It’s a family tradition that one of the children acts as Santa’s helper, delivering gifts from under the tree. Clara carefully scrubbed her hands before she put on the special helper’s hat and began racing back and forth with packages. We called Allison and Andy in Millbrook and Andrew in Halifax. In the afternoon, Sarah went off to a local hill to see the grandkids with their new sleds and I worked on dinner.

Chris was holding his own. When I checked on him in mid-afternoon, he sounded lonely and discouraged. He said the volume of the stools was definitely decreasing but they were still completely liquid and very frequent. He was still peeing a fair amount, but he never wanted to see Gatorade again. Oh – and could Sarah come up, he had another load of laundry.

Dinner was delicious with turkey and all the usual accompaniments but it was not the same without Chris, usually the life of the party. We pulled our Christmas crackers and all wore paper crowns and read each other’s jokes. We drank Prosecco and told stories about turkeys of the past. Full and warm and tired after a long day of people and presents and sledding, the kids were sleepy and they all left soon after dinner with instructions to continue very careful hand washing.

By evening, Chris said he was definitely better – stools were continuing to diminish in volume and frequency. He had been able to sleep for almost 2 hours without running to the bathroom. We sent up more Gatorade and did the dishes. Then we called Graeme to tell him about Chris and see if anyone there was sick – all were well with no hint of diarrhea.

The next morning, Chris was downstairs eating applesauce and drinking tea – the diarrhea had ended sometime after midnight. Sarah, Les, and I were all well. We made panettone French toast and then headed for home. Over the next few days, we spoke daily – Marisa sent a fabulous photograph with Marc Andre on the beach and a report of no symptoms. Rebecca emailed from Germany that the trip had gone well and no-one was sick. By Noel Deux, a week after Chris fell ill with everyone else still well, I felt safe in saying the risk of transmission was over.

The most likely cause of Chris's illness was enterotoxigenic *Escherichia coli* bacteria, but it could also have been caused by norovirus. It's hard to say we broke the chain of disease when only one person was infected, but traveler's diarrhea is highly contagious. We did follow the basic principles of disease control: early case detection and isolation; community (well, family) education and engagement; supportive clinical care; rigorous infection control; and contact tracing.

Looking back on it, without effective infection control, we did have all the ingredients for initiation of a global outbreak with immediate disease spread in five countries on three continents. And ours was not an unusual situation – for every virus we have studied, international travel played an important role in epidemic spread: it was international travelers who transported Zika from Asia to Brazil via Yap Island and French Polynesia; international travelers who carried SARS from China to 40 different countries; local travelers spread Ebola through the countries of West Africa, but international travelers carried it out of West Africa to Nigeria, the United States and Spain with the potential to establish a global pandemic; the yellow fever virus was transported by West African slaves to the Caribbean where a critical mass of viremic hosts and active vectors in a receptive environment led to centuries of recurrent epidemics throughout the Americas; returning workers carried HIV from the Belgian Congo/DRC in Central Africa back to Haiti, from Haiti to the United States and from there, all over the world; the polio virus with its long incubation period and predominantly asymptomatic infectious state can travel great distances undetected, entering polio-free areas by land, sea, or air travel – a major reason it has still eluded global eradication efforts; smallpox came to Europe from Asia and Africa during the Middle Ages via trade and migration routes and the paths of the crusaders before spreading to the Americas in the ships of Spanish and Portuguese explorers; and the dramatic global spread of the 1918 influenza virus was expedited by soldiers traveling to the European theater and then

home again. International travel played a major role in the spread of all the viral epidemics of the last century that we have studied.

And international travel is exponentially increasing. Based on airline industry data, there is exponential growth in air travel with doubling of passenger-kilometers every 15 years (a passenger-kilometer is equal to moving one person one kilometer). In October of 2017, The International Air Transport Association (IATA) announced industry performance statistics for 2016 showing that system-wide, airlines carried 3.8 billion passengers on scheduled services last year, an increase of 7% over 2015, representing an additional 242 million air trips.

In 2011, a University of North Carolina business professor named John Kasarda published a book with Greg Lindsay called *Aerotropolis: The Way We'll Live Next*. He writes: "The 18th century really was a waterborne century, the 19th century a rail century, the 20th century a highway, car, truck century – and the 21st century will increasingly be an aviation century, as the globe becomes increasingly connected by air." His prediction is reflected in airline industry data: Middle Eastern and Asia Pacific airlines posted their fastest growth in 2017; Latin American and African airlines fly a relatively small proportion of international flight volumes, but both regions saw solid increases. The challenging economic backdrop in Brazil suppressed passenger demand in recent years, but travel volumes are still trending upwards at an annualized pace of ~4% per year. All the major areas of the globe where new viral epidemics have emerged over the last century are areas with increasing air travel.

Travel bans, entry and exit screening and quarantine of returning health workers – all seen in the response to the Ebola epidemic – have not been proven effective, but efforts like this are likely to emerge again as prolific international travel makes rapid and explosive global spread of infection more and more likely. There are many other important factors in the increasing frequency of epidemics over the last century, but our Christmas outbreak is a cautionary tale and a good introduction to a look at global efforts to prevent future pandemics

A Way Forward

Viruses are formidable enemies. They are by far the most abundant life form on earth – there are billions of viruses, more than all other life forms combined, and we have only just begun to explore the diversity and extent of the earth's massive virosphere. And they are ancient, most likely the oldest form of life on our planet.¹ Despite their tiny size and simple structure, their inability to move independently, replicate or produce energy, viruses have the capacity to control our destiny. In particular, their intrinsic ability to mutate allows them to endlessly evolve into new forms with enhanced capacity to parasitize, replicate, and cause new diseases

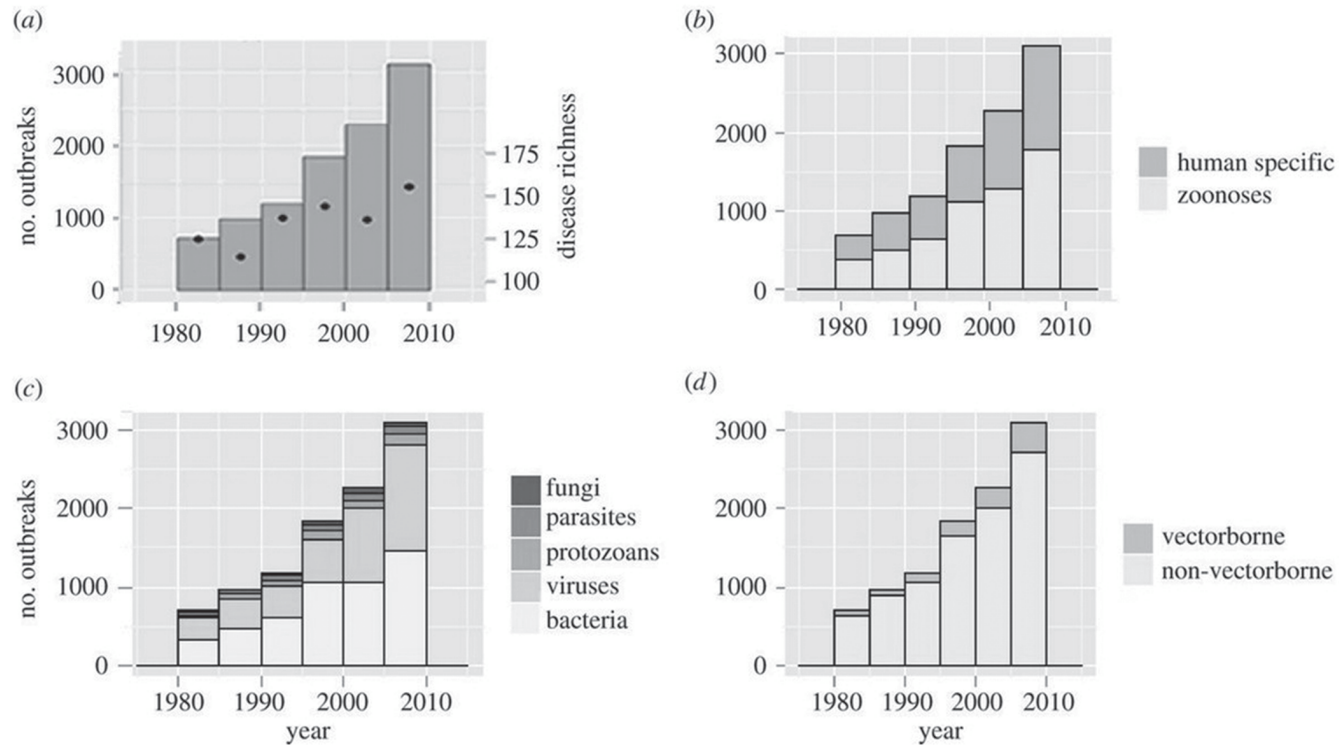


FIGURE 8.2 Global number of human infectious disease outbreaks, 1980–2010. Outbreak records are plotted with respect to (a) total # of global outbreaks (left axis, bars) and total number of diseases causing outbreaks per decade, (b) host type, (c) pathogen taxonomy, (d) transmission mode.

which can sweep through whole populations, leaving utter devastation behind. As Nobel-prize winning biologist Joshua Lederberg wrote: “The single greatest threat to man’s continued dominance on our planet is a virus.”²

In this book, we have concentrated on viruses that have caused epidemics since the beginning of the twentieth century. We have seen that emerging and re-emerging viruses are causing increasingly frequent viral disease outbreaks in people and in animals. In this chapter, we integrate the biologic and environmental factors that emerged through analysis of the pandemics in this book to create a composite picture of the state of viral infectious disease outbreaks after Ebola. To begin, a biogeographic analysis of a 33-year data set of human infectious diseases from the Global Infectious Disease and Epidemiology Network included 12,202 outbreaks of 215 different diseases.³ The analysis showed the total number of outbreaks increased exponentially between 1980 and 2014 with the greatest increase in viral pathogens and significant increases in zoonotic diseases and in both vector-borne and non-vector-borne disease.

More than 60% of the roughly 400 emerging infectious diseases that have been identified since 1940 are zoonotic, as shown in Figure 8.2. Zoonotic infections occur when a virus has a wide host range with natural hosts that are infected in a primary transmission cycle and alternative hosts which can be infected by spillover from that original species to another – influenza is an excellent example of this. An important part of the dangerous potential of viruses emerges when a virus is transmitted directly from animals to humans as seen in all but two of the pandemics that we have explored: only smallpox and polio are non-zoonotic viruses. Spillover of a virus across the species barrier to infect a human exposes an immunologically naïve subject to a potentially devastating new pathogen.

What are the factors behind this dangerous pattern of evolution?

The answer is deceptively simple: we are. Warwick Anderson describes this vision as follows:

Evolutionary processes operating on a global scale were responsible for the emergence of “new” diseases. As environments changed, as urbanization, deforestation, and human mobility increased, so, too, did disease patterns alter, with natural selection promoting the proliferation of microbes in new niches.⁴

Among the human factors considered predominantly responsible for the global increase in infectious disease outbreaks, one of the most important is increasing population density. As shown in Figure 8.3, our global population has increased dramatically in recent centuries. Between 1900 and 2000, the increase in world population was three times greater than during the entire previous history of humanity – an increase from 1.5 to 6.1 billion in just 100 years.⁵

The latest projections from the United Nations estimate that the world’s population will reach 9.6 billion people by mid-century, and 11 billion by 2100. Quite simply, diseases spread more quickly among people who live in close proximity.

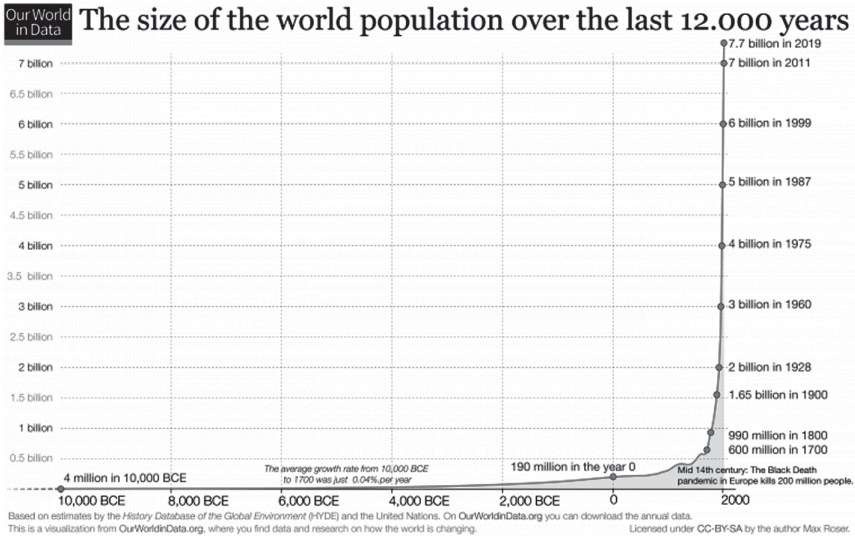


FIGURE 8.3 World population over time.

Source: Data from the United Nations.

And population growth is most rapid in areas where disease outbreaks occur most frequently, and where limited health system infrastructure can facilitate disease spread. As an example, the population of sub-Saharan Africa is increasing at more than twice the rate seen in high-income countries in the Global North in the last 70 years.

Contact rates and patterns among individuals in a geographic area drive transmission of pathogens and the higher the population density, the greater the contact rates between and among people. Because many viruses cannot survive for long outside their host environment, close proximity of hosts, or hosts and vectors, is essential for disease transmission – and this is optimized in densely populated areas. In addition to more frequent contact between individuals, interactions with animals and ecosystems are enhanced, an important factor in the rising prevalence of zoonotic diseases.⁶ Zoonotic viruses are the most frequent newly emerging human pathogens, constituting 85% of all pathogens discovered since 1980. As increasing global population density has brought wild animals and human populations into closer and more frequent contact, new infectious disease threats are often found to have wildlife origins. RNA viruses with their high rates of nucleotide substitution, poor mutation error-correction ability and therefore higher capacity to adapt to new hosts have been identified as a major threat for cross-species infection. Reservoir hosts – like the bat shown in Figure 8.1 – are also encouraged by close proximity to potential disease hosts: viruses cannot survive independently, but they can be sustained in asymptomatic animal hosts who represent an ongoing source of infection and of genetic material for the emergence of novel zoonotic pathogens.

Increasing urbanization parallels increasing population density. Only 3% of the world's population lived in urban areas in 1800; this proportion had risen dramatically to 50.5% by 2010; more than half of the world's population now lives in cities and this proportion is predicted to steadily increase.⁷ In urban areas, more frequent contact between more individuals drives infection with directly transmitted disease pathogens. In addition, urbanization increases the preferred habitat for anthropophilic disease vectors like *Aedes aegyptii* and *A. albopictus*, the mosquito vectors for the Zika and yellow fever viruses. Increasing vector capacity increases potential disease transmissibility.

High population density and/or urbanization played significant roles in all the epidemics we have studied.

- From its first appearance in the fourth century BCE, smallpox was most prevalent where people clustered together, enhancing person-to-person spread of the virus.⁸
- Yellow fever outbreaks in North America were concentrated in port cities where the virus had been transported from the Caribbean and where reservoir host mosquitoes and access to vulnerable humans maximized disease transmission.
- With the 1918 influenza pandemic, the close proximity of military recruits and soldiers during training, transport, and engagement in World War I contributed significantly to global disease spread. And pneumonia death rates in the USA were highest in cities and higher-population areas.⁹
- Polio outbreaks clustered in urban areas and in locations like schools, swimming pools, and summer camps where contact between infected people – especially children – was high.
- The human immunodeficiency virus, HIV, originated in nonhuman primates in Central and West Africa early in the twentieth century. These viruses are thought to have crossed over into humans sporadically for a long time, most likely related to hunting and butchering monkeys and chimps. Those ancient infections never spread because human population density in the area at that time was so low – it was only when the virus traveled to Kinshasa, the capital of the Democratic Republic of the Congo, at a time of explosive population growth that the HIV/AIDS epidemic started. In the early years in North America, AIDS was almost exclusively an urban disease, reflecting the density of the gay populations and IV drug users at highest risk.
- SARS-CoV was primarily transmitted by respiratory droplets when an infected person coughed or sneezed – a pattern that was obviously enhanced by close human contact in areas with high population density.
- The West Nile virus pandemic exploded in NYC where large populations of immunologically naïve people, reservoir birds, and vector mosquitoes all clustered together.
- The dramatic spread of Zika in 2015 reflected both the high Brazilian population density and the location of the anthropophilic *A. aegyptii* mosquito.

- Bats are the natural reservoir of the Ebola virus, which can be transmitted directly to humans or indirectly via an infected wild animal – usually a monkey, chimpanzee, baboon, or gorilla, with transmission related to hunting or butchering these animals, reflecting necessary proximity of animal and human populations. Rapid early spread of the Ebola epidemic in 2014 is at least partially attributed to the high population density and proximity to urban centers in West Africa compared with previous outbreaks in central Africa.

Deforestation is another important factor in the global increase in infectious disease. The human activities that drive deforestation – logging, slash and burn commercial agriculture, mining, logging for firewood, subsistence farming, and road construction – all bring forest and jungle animals and people closer together. Deforestation forces wildlife of all kinds, from insects to giant apes, to find new habitats closer to human civilization. Guinea, where the 2014 EBOV outbreak began, is a good example: it has lost 20% of its forests since 1990. Loss of primary forest can also lead to changes in the microclimate with enhancement of vector capacity. Zoonotic risk has consistently been shown to be elevated in forested tropical regions experiencing land-use changes.¹⁰

Global travel and migration are among the most important factors amplifying viral disease spread in the last century. In our highly mobile world, more than half a million travelers are in the air at any one moment. As described in the essay that opens this chapter, travelers carry diseases with them and global travel is increasing exponentially. Higher travel speed and increasing frequency mean that outbreaks that would have otherwise been contained can instead move rapidly into uninfected regions, carried by infected people. The establishment of new travel routes between previously unconnected areas allows direct pathogen spread where none existed before. Travel, both local and international, played a major role in the historic spread of all the viral pathogens of the last century. The frequency and speed of contemporary air travel has exponentially increased global connectivity and dramatically exacerbated viral disease outbreaks.

Finally, climate change plays an important role in enhancing disease spread. As temperatures increase, the mosquito and tick vectors of diseases like malaria, Zika, and yellow fever expand their range, moving into regions where they previously could not survive. Seasonal behavior of birds is altered by rising temperatures with loss of normal winter migration in some; in others, migration paths are moving further south and west as global temperatures rise, increasing the area for potential disease spread. Changes in the behavior of bird populations are important ongoing factors in the global spread of influenza and West Nile fever.

Increases in extreme weather events – an established element of global warming – may also lead to increases in infectious disease outbreaks as seen in the wake of natural disasters, associated with displaced and crowded populations, ideal for infection transmission. Severe rainfall or flooding with secondary standing water is particularly effective at creating environments suitable for the transmission and propagation of viral infectious diseases. Increased variation in weather patterns can

result in changes in human and animal interactions, increasing the potential for zoonotic pathogens to move from animals into human populations. For example, food scarcity brought about by drought may lead to increased bushmeat hunting, the original virus transmission event from animals to humans for HIV and often the initiating event for recurrent outbreaks of Ebola.

There is a strong case for the importance of environmental factors in viral disease spread. But in this book, we tell the stories of nine viruses whose unique disease narratives were determined primarily by the characteristics of the viral pathogen, in the context of scientific, medical, societal, and environmental change. As a reminder:

The story of smallpox – “the most terrible of the ministers of death” – is considered by many to be a scientific and medical triumph: it is the story of how an effective vaccine and an intrepid scientist wiped a horrible disease from the face of the earth. But it is actually the characteristics of the virus itself that made eradication possible. And despite this success, the virus lives on in research laboratories, where it is consistently identified as one of the most dangerous potential biologic weapons of mass destruction,

With yellow fever, intrepid early scientists in the jungles of Cuba and Central Africa discovered that the yellow fever virus hides in small jungle primates and is carried by people-friendly mosquitoes to cause repeated disease outbreaks in populated areas. Despite the early development of an effective vaccine, the yellow fever virus still emerges to cause repeated epidemics.

Influenza, the mercurial, ever-changing virus that caused a true global pandemic a hundred years ago, is the model of an evasive pathogen. It was more than 30 years before the importance of the capacity of the virus for constant mutation was recognized as a critical part of its pathogenicity. Carried by water birds, a newly mutated influenza virus can travel anywhere global flyways go. The combination of a stable but mobile reservoir, multiple animal hosts and the capacity for endless mutation and recombination means global populations are repeatedly unprotected from a novel influenza virus infection, either by previous exposure or by existing vaccines.

The inspiring polio narrative also reflects the power of the biology of the virus. It is the story of a terrifying virus that attacked primarily children – and an American president – leaving them permanently paralyzed. Despite identification of the virus in 1910, it was decades before it was recognized how highly contagious and infectious the poliovirus is. To this day, the global effort to eradicate polio is still deterred by the capacity of the virus for spontaneous mutation.

That HIV has caused the longest continuous pandemic in world history directly reflects the complex biopathology of this virus. Its capacity to lie hidden in host cells allows progressive destruction of the body's immune system before AIDS emerges. This asymptomatic carrier state allowed the pandemic to expand exponentially before it was even recognized; it was also a critical factor in the delayed development of effective treatment. The extremely rapid mutation rate of the virus consistently frustrates vaccine development efforts. Enormous progress has been made with combined antiretroviral treatment, allowing infected individuals to live

a normal life span. There remains a major biologic barrier to HIV eradication: the persistence of integrated replication-competent HIV reservoirs in memory CD4+ T cells which emerge whenever antiretroviral treatment is stopped and to this time, have completely prevented eradication.

No emerging disease narrative better exemplifies the power of the pathobiology of an unknown virus than the WNV, which established host reservoirs in local bird flocks from which mosquito vectors perpetuated the infection, incidentally infecting naïve human hosts and spreading rapidly throughout the entire Western Hemisphere. Failure to recognize the mutation-acquired neurotropic potential of this virus allowed it to become the leading global cause of neuroinvasive disease.

The SARS coronavirus emerged from caves in China in late 2002, carried by horseshoe bats via intermediate hosts to infect thousands of people over a 6-month period. During that short time, oblivious, infected individuals carried the virus on airplanes to all corners of the globe. The sudden emergence of a novel pathogen from an animal reservoir allowed global spread to occur before the virulence of the virus was recognized.

Zika was an apparently innocent virus until spontaneous mutation created neurotropic characteristics that were devastating to thousands of unborn babies. Its new virulence was unrecognized until it was carried into large, densely packed populations of immunologically naïve people and the mosquito vector that transmits the disease.

The Ebola virus (EBOV) was known to scientists for more than 40 years as a pathogen that caused small outbreaks of hemorrhagic fever with a very high mortality rate in Central Africa. Although EBOV is not highly contagious, it is very highly infectious, with blood exposure to even a single virus resulting in infection. In 2014, it emerged from relative obscurity to cause a massive outbreak in a large naïve population that lasted more than two years. The EVD pandemic revealed just how vulnerable we are to a virulent pathogen that spreads rapidly in an immunologically defenseless population.

These fascinating and terrifying narratives show us how dangerous viruses can be. They show us doctors and scientists battling to respond to invisible enemies they are struggling to understand. These are stories of devastating illness and miraculous scientific breakthroughs, amid ongoing efforts to end diseases that emerge and re-emerge to cause devastating losses all over our interconnected planet. Time and again, the viruses themselves outwit our best efforts to subdue or erase them.

Combined with the pathogenic characteristics of the viruses, critical environmental and societal factors have potentiated a steady increase in the frequency and severity of viral disease outbreaks over the last century. With unprecedented increases in population density and global mobility, climate change and deforestation, diverse disease pathogens like these are increasingly widespread, mobile and transmittable. Ever-increasing global connectedness means no nation is immune to the growing threat posed by an outbreak of an unknown infectious virus in a remote part of the world. Vigilant and effective health systems are needed to allow

countries to detect and respond to these pathogens and prevent an infectious disease outbreak from becoming a pandemic.

A Way Forward

In this section, we evaluate all the pathogens as a group, looking for common themes that can be used to develop ways to prevent the emergence of new infectious agents as epidemic threats in the future and to improve the outcome when new outbreaks occur. We begin with an overview of international health agencies – option one of this analysis – starting with the WHO. The extensive critical review of the WHO response to the 2014–2016 Ebola epidemic provides a useful starting point – it has been described as a “transformative event in global health,” with independent assessments by the World Health Organization itself, the Center for Disease Control and Prevention (CDC), the United Nations, the Harvard/London School of Hygiene and Tropical Medicine Independent Panel and the National Academy of Medicine, among others.¹¹ Most analyses referenced failure to achieve the classical public health standards for controlling a disease outbreak – ongoing surveillance; case detection and isolation; effective clinical care; strong community engagement and education; comprehensive contact tracing and quarantine; rigorous infection control – as critical performance failures. We will also develop alternative ways to transform future disease outbreaks.

The WHO is the designated health branch of the United Nations and is considered by many to be the guardian of global health and security, empowered since 1948 by its constitution to prevent the international spread of disease. Initially, this role was confined only to management of outbreaks of cholera, yellow fever and the plague, as defined by the original International Health Regulations (IHR). Practically speaking, in the event of any major infectious disease outbreak, the world has always looked to the WHO to lead the global response.

The decision-making body of the WHO, the World Health Assembly (WHA), meets annually, attended by delegations from 193 Member States; we encountered the WHA in the chapter on smallpox when they approved the global smallpox eradication program. In 1995, in a delayed response to the steady spread of HIV/AIDS, the WHA first called for revision of the IHR to address global infectious disease threats. With the SARS epidemic in 2002–2003, there was further pressure for IHR reform which finally resulted in the revised IHR (2005) which became effective in 2007.¹² The revised regulations aim to “prevent, protect against, control and provide a public health response to the international spread of disease.” They include specific measures to limit the spread of health risks to neighboring countries while minimizing travel and trade disruption. The IHR also include an algorithm for assessment of events that might constitute a public health emergency of international concern (PHEIC), defined as “an extraordinary event which is determined . . . to constitute a public health risk to other States through the international spread of disease; and to potentially require a coordinated international response.”¹²

Compared with the previous relatively narrow focus on specific diseases, the new IHR define disease very broadly as “all illnesses or medical conditions, irrespective of origin or source that could present significant harm to humans” – a major increase in the WHO’s scope of responsibility, intended to initiate global cooperation in disease preparedness. According to the legal scholar David Fidler, the 2005 IHR revision was “one of the most radical and far-reaching changes in international law on public health since the beginning of international health co-operation in the mid-nineteenth century.”¹³ Unfortunately, this substantial increase in responsibility was not accompanied by any change in structure or funding; in fact, member states voted to decrease the WHO’s budget by 13% in 2011 with specific cutbacks in the outbreak and emergency response departments. The process for declaration of a PHEIC was entirely new and unfamiliar; by 2014, it had only been utilized twice with critical, mixed responses from the international community. Major inadequacies in existing national healthcare infrastructure systems were identified as significant liabilities for surveillance, detection, and control of disease outbreaks – these are defined as “core capacities” by the IHR. Nonetheless, the substantial delay in the PHEIC declaration which finally brought the Ebola epidemic to international attention 5 months after the first case was consistently identified by independent reviewing bodies as an important failure.

The IHR are a legally binding agreement between the 196 WHO signatories including all Member States and Strategic Partners who are contractually bound to build their individual country’s core capacities – the healthcare infrastructure and workforce necessary for disease surveillance, detection, and outbreak control. The original deadline for development of these core capacities was 2012, but there have been repeated delays with only a minority of WHO member states meeting minimum IHR capacity benchmarks. While theoretically appropriate and essential, development of the core capacities requires national political support and funding. Of note, Guinea, Liberia, and Sierra Leone are all WHO Strategic Partners – but as revealed by the Ebola outbreak, none had yet developed anything close to the required healthcare infrastructure. Finally, in a public health emergency like the Ebola outbreak, even a well-equipped healthcare infrastructure and a well-trained workforce can be overwhelmed and the WHO had no access to an emergency response team to deal with this circumstance. The delay in declaring the Ebola epidemic a PHEIC, failure to insure development of core capacities in Member States, and the absence of a funded emergency response network were identified as critical WHO failings in analyses of the Ebola epidemic.¹¹ Theoretically, the new broadened scope and required national healthcare infrastructure core capacities of 196 countries give the WHO the opportunity to lead a well-equipped global public health team. The deficiencies of the Ebola performance, however, suggest that the WHO is not prepared to respond to a major large epidemic. Critical reviews underline the divide between what the global community expects the WHO to do in every health crisis and what it is able to do with its current organizational and financial constraints.

In response, the WHO has developed a comprehensive plan to address the identified inadequacies,^{14–16} beginning with development of a separate Health Emergencies (WHE) program with defined organization-wide guidelines for infectious hazard management, organization and assessment of member state preparedness and emergency information management, supported by rapidly accessed financial support. A single program, with one workforce, one budget, one set of rules and processes and one clear line of authority is seen as a critical step forward. Led by a newly appointed Executive Director, the WHE Program is intended to handle operations for all emergencies. As part of the WHE program, WHO is creating a global health workforce to provide surge support to national health systems through their Regional Organizations, delivering clinical care to emergent disasters and outbreak-affected populations. By May 2016, 64 countries had either successfully launched teams or were in the process of accreditation to be members of this workforce.

Recognizing that national public health services – a country's existing health care infrastructure – are the critical first line of disease defense, the IHR (2005) requires member countries to be prepared for disease outbreaks. The WHO has developed a new system to verify compliance with the mandated core competencies for surveillance, detection, and control of disease outbreaks. In February 2016, WHO adopted the Joint External Evaluation (JEE) tool as a core element of the new monitoring and evaluation framework for the core competencies. The tool systematically evaluates the required IHR technical areas in national healthcare infrastructure by country, to identify the most urgent needs and prioritize efforts to enhance preparedness, response and action, and engage partners in targeting resources in the most effective way. Sixty-seven JEEs have been conducted in six regions so far with 31 JEEs scheduled for 2019.

Disease surveillance failure is a critical inadequacy. Going forward, in-country surveillance activities will be integrated with components of national healthcare systems so that data collection and analysis are immediately available. To achieve this, innovations in data collection will be introduced, potentially including geo-spatial mapping, mHealth communications, and platforms for self-monitoring and reporting. Stronger collaboration between private and public sector actors is planned to take this forward. Finally, the WHO will work with the World Bank to develop a Pandemic Emergencies Fund to be used to facilitate the response to large-scale crises due to high-risk infectious threats.

This new program is a profound change for the WHO, imposing sweeping new global operational responsibilities. In addition to its traditional role of coordinating the international response to containing disease outbreaks and providing effective relief and recovery to affected people, the WHO will now work directly with countries on development of the core capacities that comprise the healthcare infrastructure necessary for surveillance, case detection, patient care, and disease preparedness. Progress is being monitored by a UN-based Independent Oversight and Advisory Committee. At the 70th World Health Assembly, the Committee reported that significant progress had been made in multiple areas including establishment of the WHO

Health Emergencies Program and initiation of the global health workforce. Progress in developing national healthcare infrastructure through the core competencies was underway. The review concluded that the WHO is “making efforts at all levels to transform itself into an operational organization in emergencies,” but that progress is fragile.¹⁷

The WHO’s response to discovery of the limitations uncovered by the Ebola epidemic is potentially transformative but very challenging. If fully implemented these planned “top-to-bottom” changes will dramatically improve WHO’s epidemic responsiveness at both the macro-operational and member nation levels, but three years after the full-blown Ebola epidemic ended, substantial change is still an evolving process.

The Global Health Security Agenda (GHSA) is another major player in global infectious disease management. The GHSA was launched as a joint American effort of the CDC, Department of Defense, and the US Agency for International Development (USAID) in February 2014 to make global health security a national priority and galvanize prevention, detection and control of disease outbreaks at their source anywhere in the world, strengthening both global and country capacity.¹⁸ Through a partnership of nearly 70 nations, international organizations, and non-governmental stakeholders, GHSA is facilitating collaborative, capacity-building efforts to achieve measurable targets around biological threats, while accelerating achievement of the IHR core capacities – the competence of existing national healthcare infrastructure for surveillance, disease detection, patient care and control of disease outbreaks.

Within the GHSA, the CDC is working with 31 member countries to help them achieve IHR competency by developing “Action Packages” which focus on building a specific healthcare infrastructure competency. By providing educational training and measurable steps to 5-year targets, the action packages are designed to help nations steadily progress with specific indicators that can be used to measure how healthcare infrastructure has developed and how it can be maintained over the long term. Practical training like this should allow member countries to progress towards the healthcare infrastructure core capacity surveillance target with a 5-year time line. An interim analysis of CDC-supported efforts to achieve IHR core capacities and GHSA targets for health care infrastructure development between April 2015 and March 2017 showed that CDC helped 17 countries to achieve 675 major GHSA accomplishments, particularly in the cross-cutting areas of public health surveillance, laboratory systems, workforce development, and emergency response management.¹⁹ As ongoing WHO evaluations reveal, these improvements in healthcare infrastructure have only rarely resulted in full IHR competency.

During the 2014 Ebola outbreak, the CDC played an important role as the medical lead for the international response, helping with infection control, contact tracing, laboratory surveillance and training and augmentation of emergency operation centers. CDC has also been involved in the conduct of clinical trials in

affected countries to assess the safety and efficacy of vaccine and drug treatment candidates. The GHSA trained almost 25,000 healthcare workers on site in West Africa and 159,000 US healthcare workers by webinars and calls; screened more than 270,000 travelers leaving a country with widespread transmission for Ebola; enrolled 8650 People in the STRIVE Ebola vaccine study and performed more than 26,000 Ebola laboratory tests.

The United Nations Children's Fund (UNICEF) is a major player in child health initiatives. The organization prioritizes the needs of the world's most vulnerable children, especially in areas of critical unrest. UNICEF was on the frontlines in Ebola-affected countries, helping to contain the spread of the disease and address communities' most urgent needs, including restoration of water and sanitation and basic social services. For the long term, UNICEF continues to work to support child and maternal health, nutrition services, education, and social welfare all over the world.

Non-governmental organizations (NGOs) and humanitarian groups are a critical component of the response to disease outbreaks. A subset of NGOs focus their efforts exclusively on medical support. Chief among these is Médecins Sans Frontières (MSF), the medical aid group that has been providing emergency assistance since 1971, in the aftermath of natural disasters like the earthquake in Haiti, in war-torn areas like Syria and in major disease outbreaks all over the globe. MSF were on the ground in Guinea in March 2014, before any other group; in fact, it was cultures sent by MSF that identified the outbreak as EVD. They sounded the alarm about the expanding outbreak and it was repeated calls for help from MSF members that eventually led to involvement by the WHO. Before the Ebola pandemic ended in January 2015, MSF had provided critical care to more than 7000 patients in all three countries. MSF is symbolic of a number of medical humanitarian groups including CARE, the International Committee of the Red Cross, Oxfam International, and Project Hope. While their medical aid efforts like the MSF mission in West Africa provide critical assistance in times of crisis, their focus is on emergency interventions, not the development of long-term programs as part of a sustainable public health system. Their commitment to the provision of emergency medical assistance wherever it is needed is an important and laudable goal – it is easy to imagine how much worse the Ebola pandemic would have been without the involvement of MSF. However, developing the facilities and training the staff to provide a sustainable healthcare infrastructure is beyond the scope of their mission.

Option Two: Epidemiologic Analysis of Viral Epidemics of the Last Century

An alternative approach to evaluating the current state of epidemic preparedness to prevent future disease outbreaks is to look at the epidemics we have studied, using the standard epidemiologic framework for detecting and controlling outbreaks: ongoing surveillance, early case detection and isolation; community

education and engagement; comprehensive contact tracing and quarantine; clinical care; and rigorous infection control. When we did this, four themes emerged:

1. Constant Vigilance: Current Status

Public health surveillance is the ongoing, systematic collection, analysis, interpretation, and dissemination of data about a health-related event for use in public health action to reduce morbidity and mortality and/or to improve health.²⁰ Surveillance serves multiple public health functions but our focus is on outbreak detection – identifying and verifying an increase in the frequency of a disease above its background occurrence. Traditionally, surveillance has been relatively slow and passive with outbreak recognition based on accumulated case reports of reportable diseases, or by clinicians and laboratories who alert public health officials about clusters of diseases. If you remember, this was how the first stage of the influenza pandemic was identified in 1918 and how the first clinical cases of AIDS were reported in 1981. By contrast, new surveillance systems analyze electronic data to recognize patterns indicative of a possible outbreak – this includes different types of data like healthcare product purchases, work or school absences, presenting symptoms to a healthcare provider or laboratory test orders that can signify an outbreak earlier in its course.

Effective surveillance leads to prompt disease identification and initiation of an outbreak response, but to be effective, surveillance systems must be accurate, timely and complete – all significant challenges in resource-poor areas. The parts of the world that are most vulnerable to emerging disease threats often lack essential surveillance infrastructure; the existing patchwork of traditional surveillance efforts managed by health ministries, public health institutes, multinational agencies, and laboratory and institutional networks often has wide gaps in geographic coverage and poor information flow across national borders.²¹ In a review of emerging infectious disease threats, Director Anthony Fauci and his team from the National Institute of Allergy and Infectious Disease identified optimization of global surveillance to detect outbreaks early as the number one priority.²²

In the Ebola outbreak, the absence of core surveillance capabilities in Guinea, Sierra Leone, and Liberia was critical in the delayed recognition of EVD and its early exponential spread through the three countries. With HIV/AIDS, surveillance efforts in the United States were effective in identifying the emergence of a new disease, but an almost exclusive focus on a marginalized segment of the population delayed a full-scale response to the epidemic; recognition of the disease where it originated in central Africa was also substantially delayed and this allowed extensive global spread to occur.

Constant Vigilance: Progress/Potential

An enormous amount of valuable information about infectious diseases is found in Web-accessible sources like disease reporting networks, news outlets, and social

networking sites. These resources can provide current, local information about outbreaks, even from areas that are relatively invisible to traditional global surveillance methods. The data hold tremendous potential to provide real-time epidemic intelligence, complimentary to traditional surveillance sources. A number of countries and organizations have developed programs to optimize outbreak detection by using online resources for real-time biosurveillance and case detection at ground level. These include ProMED mail, an official, funded program of the International Society for Infectious Diseases. Launched in 1994, ProMED mail links volunteer experts in human, plant, and animal disease to 83,000 volunteer subscribers in more than 200 countries who post media reports, online summaries and local observer reports to a public website using email. Moderators screen reports to highlight the most important events. ProMED reports globally 24/7/365, averaging eight outbreak reports per day. Their networks and moderators include three sites in Africa and one in south Asia. In a published review of digital surveillance systems, ProMED scored in the top two for its ability to detect disease outbreaks before their publication in a standard weekly epidemiology bulletin like *MMWR*. In 2016, ProMED launched EpiCore, a global team of trained volunteer epidemiologists and health professionals who report and validate suspected outbreaks in their own communities in response to requests for information from ProMED operators. ProMED was one of the first outlets to identify SARS in 2003, undiagnosed hemorrhagic fever (later identified as Ebola) in Guinea in 2014, and early Zika spread in the Americas in 2015.²³

The Global Public Health Intelligence Network (GPHIN) developed by Health Canada is a federally funded, secure Internet-based multilingual early-warning tool that continuously searches global media sources such as news wires and websites to identify information about disease outbreaks and other events of potential international public health concern. More than 60% of initial outbreak reports come from unofficial informal sources, including sources other than the electronic media. GPHIN was established to increase situational awareness and capacity by using “Big Data” for the early detection of emerging public health events. GPHIN daily analyzes more than 20,000 online news reports in nine languages worldwide. A web-based program aggregates data based on an algorithm that provides potential signals of emerging public health events which are then reviewed by a multilingual, multidisciplinary team. An alert is sent out if a potential risk is identified. The GPHIN identified the early SARS outbreak in China, was credited with the first detection of MERS-CoV, and played a significant role in monitoring the Ebola outbreak in West Africa.²⁴

HealthMap (www.healthmap.org/) is an American multistream real-time surveillance platform that continually aggregates reports on new and ongoing infectious disease outbreaks and displays them on a global map. It is funded by a combination of public and private sources including Google, Unilever, Defense Threat Reduction Agency, Skoll Global Threats Fund, USAID, the Canadian Institute for Health Research, and the Bill & Melinda Gates Foundation. Updating 24/7/365, the system monitors, organizes, integrates, filters, visualizes, and disseminates online

information about emerging diseases in nine languages, facilitating early detection of global public health threats by utilizing online informal sources for disease outbreak monitoring and real-time surveillance of emerging public health threats. The system currently serves as a direct information source for ~20,000 unique visitors per month, as well as a resource for libraries, local health departments, government agencies (e.g., the US Department Health and Human Services, CDC), and multinational agencies (e.g., the United Nations, WHO), which use the HealthMap data stream for day-to-day surveillance activities.²⁵

The Global Outbreak Alert and Response Network (GOARN) was established in 2000 to provide operations and logistics platforms for any WHO response to international public health risks.²⁶ GOARN's infrastructure united more than a hundred existing networks which are supported by a computer-driven tool for real-time gathering of disease intelligence. Formal and informal information sources are combined with ~65% of outbreak information coming from informal sources. GOARN electronically links leading laboratory scientists, clinicians, and epidemiologists around the world in a virtual network that can rapidly generate and circulate knowledge about emerging pathogens and outbreaks. When a significant public health event takes place, GOARN coordinates information from multiple sources to provide event-based surveillance, rapid risk assessment and communication, and critical information platforms for decision support and response coordination. GOARN has provided an operational framework for the WHO to respond to major outbreaks of cholera, dengue, encephalitis, influenza, meningitis, plague, SARS, Ebola, and yellow fever.

Several programs address the need to develop surveillance capacity at the local level including the Pandemic Influenza and Other Emerging Threats Unit of USAID. Since 2005, USAID has worked to strengthen the capacities of more than 50 countries to monitor the spread of H5N1 avian influenza among wild bird populations, domestic poultry, and humans; to mount a rapid and effective containment of the virus when it is found; and to help countries prepare operational capacities in the event a pandemic-capable virus emerges. Efforts are focused in China, Indonesia, Vietnam, Bangladesh, and Egypt, primary reservoir sites for the virus. The USAID Emerging Pandemic Threats program was launched in 2009 to aggressively pre-empt or combat diseases that could spark future pandemics. Four complementary projects operate in 20 countries with technical assistance from the CDC. The EPT global program draws on expertise from across the animal and human health sectors to build regional, national, and local capacities for early disease detection, laboratory-based disease diagnosis, rapid response and containment, and risk reduction.²⁷

Based on the agency's extensive experience with 2-year programs that train field epidemiologists in place, the CDC developed the Frontline Field Epidemiology Training Program (FETP) which was launched in 2015, in response to the Ebola epidemic. These are 3-month field training programs targeting local Ministry of Health staff, designed to strengthen surveillance and improve the response to public health threats at the country level, specific to each country's needs. The overall goal

is to increase local field epidemiology capacity in areas where this is needed most. As of December 2016, FETP-Frontline had trained 1354 graduates in 24 countries, the majority in Africa and southern Asia. A recent analysis of the program identified major improvements in timeliness and accuracy of district-level surveillance reporting, critical gaps uncovered by the Ebola outbreak.²⁸

The results of optimized, on-the-ground surveillance combined with ongoing internet surveillance from programs like these integrated with real-time information on geography and travel patterns can create global maps that allow the earliest visualization of potential new disease outbreaks. This shift to use of the internet and digital epidemiology combines the classic “shoe leather,” on-the-ground techniques implemented by John Snow in his study of cholera with high-level informatics to forecast disease outbreaks and prevent future pandemics. Surveillance systems like those described here provide routine surveillance data to multilateral, multinational agencies which analyze and disseminate information on disease trends at the regional and global level. These agencies also share data from other countries when the impact of a public health event crosses national borders, a standard of practice codified by the 2005 International Health Regulations, the international legal instrument aimed at assisting the global community to prevent and respond to public health threats that have the potential to affect populations worldwide.

II. Know Your Enemy: Current Status

Early disease detection and identification is a critical early step in outbreak detection, but this is often substantially delayed because of gaps in knowledge about the infectious agent. Understanding the lethality, transmissibility, mutability, and clinical pattern of a virus informs all aspects of the response to disease detection. An obvious example: during the Ebola outbreak, failure to recognize early cases of the disease caused a substantial delay in outbreak response. HIV/AIDS is another good example: as this epidemic unfolded, engagement of the scientific community lagged behind, related to politically driven decreases in national funding for scientific research and societal bias against homosexuality.²⁹ The epidemic had been in full swing for at least 5 years before it was recognized that infected individuals had asymptomatic latent disease for an average of 10 years before the overt AIDS picture emerged. Once it was understood that progressive destruction of the immune system was ongoing during all of this time, research could be directed at an effective approach to treatment – albeit, 15 years after the first cases emerged, a global pandemic was well established and almost a million people had already died. Another HIV/AIDS knowledge gap: infected individuals are known to harbor hidden reservoirs of latent HIV-infected cells that allow persistence of the virus in a non-replicating state. Only recently has the reservoir for latent HIV been identified as a subset of CD4+ T lymphocytes called resting memory cells that are widely distributed throughout the body. HIV reservoirs explain the impossibility of complete HIV eradication to this time, so ongoing research can now be focused on

developing methods to reverse latency and then rapidly eliminate the reactivated virus population. Another example: yellow fever caused recurrent epidemics for several centuries in the Americas with thousands of deaths until the early 1900s before it was recognized that the disease was transmitted by mosquitoes – control of the vector led to dramatic early decreases in the disease. The recent Zika pandemic is another example of incomplete understanding of the virus severely delaying recognition of the neuropathology associated with fetal infection. It is 15 years since the international SARS outbreak, but this virus may well be still circulating in an animal reservoir. Increased understanding of the molecular biology of SARS-CoV discovered after the pandemic ended will be critical information should clinical disease appear again.³⁰

These examples reinforce the concept that there is no substitute for sound, complete epidemiologic, microbiologic, pathophysiologic, and molecular biologic knowledge of a disease pathogen. Definitive scientific investigation of the infecting pathogen must be a critical early and ongoing focus in any outbreak.

Know Your Enemy: Progress/Potential

The Ebola epidemic highlighted the importance of research to provide critical knowledge about a virus as an integral element of the epidemic response. Although Ebola was first identified in 1976, disease outbreaks had been sporadic and relatively small and had occurred in areas where healthcare resources are extremely limited; research had therefore been relatively minimal before 2014 when this major outbreak began. But in May 2014 when the epidemic in West Africa was dramatically expanding, Sabeti Paradi and her team sequenced 99 Ebola virus genomes from patients in Sierra Leone, demonstrating rapid accumulation of interhost and intrahost genetic variation that allowed them to characterize patterns of viral transmission on the ground in the initial weeks of the epidemic.³¹

Despite formidable obstacles, other researchers investigated a number of different care protocols and diagnostic tools including methods to perform rapid, deployable, point-of-care diagnostics. These include a proficiency panel for the molecular detection of EBOV developed in collaboration with the Robert Koch Institute in Germany and a mobile field laboratory which provides the capability to rapidly test samples on site and focus support and follow-up on new laboratory-confirmed cases and their contacts. The mobile laboratory was a core element in the Ebola epidemic and will help to provide robust surveillance in future outbreaks in remote and resource-poor settings.³²

Just as importantly, in the heart of the epidemic, researchers initiated efforts to develop a vaccine to prevent and or/limit future outbreaks. A collaborative global effort coordinated by the WHO resulted in accelerated development of a number of candidate vaccines against potential pathogens, funded by international philanthropy. Viral vectors previously identified as safe in human studies for other candidate vaccines were fast-tracked and two were studied in clinical trials during the epidemic. One of these, a replication-competent vesicular stomatitis virus (rVSV)

model, was studied in a trial involving 11,841 people in Guinea in 2015. The rVSV vaccine had no severe safety concerns and was shown to be 100% efficacious and 75% effective at the cluster level, including demonstrated herd immunity in unvaccinated cluster members. On the basis of this success, the rVSV vaccine was used on an expanded access basis in March 2016 in response to a new outbreak of EVD in Guinea and more recently in two EBOV outbreaks in the DRC in 2018. An innovative ring vaccination strategy was used based on the technique developed and proven effective during the smallpox eradication campaign with aggressive surveillance for EVD cases and contact tracing and vaccination of all contacts and people at risk. The rVSV vaccine has proven to be highly effective after a single dose when used in this way: no secondary cases of EVD developed among those vaccinated and there were no serious adverse events. The National Academy of Sciences has described the Ebola vaccine experience as a model for development of future viral vaccines and the WHO has published a research and development blueprint which provides protocols for development of diagnostic techniques, therapeutic medications and preventive vaccines for prioritized pathogens in potential, future viral outbreaks.^{33,34} The Coalition for Epidemic Preparedness Innovations (CEPI) is continuing to prepare selected vaccine candidates and to develop vaccine platforms to be used with a specific pathogen when needed. All these methods hold promise for accelerated vaccine development in response to emerging disease threats.³⁵ Complete epidemiologic, microbiologic, pathophysiologic, and molecular biologic knowledge of a disease pathogen is crucial for optimal prevention, detection and management of any infectious disease outbreak. Definitive scientific investigation of the infecting pathogen must be an early and ongoing goal in any outbreak, with a focus on the discovery and production of new vaccines, diagnostics and therapeutics.

III. The Homefield Advantage: Healthcare Infrastructure and Community Involvement for Epidemic Preparedness – Current Status

A robust national healthcare system including local community preparedness is the critical first line of defense against epidemic threats. Disease outbreaks typically erupt at the community level and communities are key drivers in the persistence and transmission dynamic of infectious diseases. The most vulnerable communities are often located in isolated, remote, rural areas that are hard to reach so the local healthcare system is the first line of defense. Unfortunately, many serious disease outbreaks have occurred in resource-poor areas with neither a strong healthcare infrastructure nor community involvement. The 2014–2015 Ebola epidemic in West Africa exemplifies this situation.

The epidemic began in Guinea, which has one of the weakest health system infrastructures in the world. Before the outbreak, the health workforce density (physicians, nurses, midwives, dentists, pharmacists, and psychiatrists) was less than 1.5 per 10,000 population, with a total of three hospital beds per 10,000 population. The per-capita government expenditure on health was only 9 US\$ per year. The infant

mortality rate was one of the highest in the world. The situation was similar in Liberia and Sierra Leone where the disease spread. Clearly, the public health system infrastructure lacked the primary essential elements required to control an outbreak.³⁶

The index case occurred in a small village in a densely forested area with no electricity and no reliable communication system. In addition, as in many outbreaks, the healthcare pathway started with a single community healthworker in a nearby village who lacked any knowledge of Ebola: from the outset, disease spread was guaranteed within the family, the community and the area. In the absence of a functioning health system with a network of laboratories, Ebola spread rapidly, undiagnosed, for almost 4 months. When patients did encounter healthcare workers, they had neither the training nor the supplies needed to manage Ebola cases, and they were completely unprepared to control the spread of infection, lacking the necessary knowledge and equipment. Patients who did reach hospitals were not isolated so the disease spread within clinics and hospitals. Healthcare workers – like the first community healthworker near Meliandou – were among the first to contract the disease and die. For frightened patients, existing health services became associated with disease and death. The WHO document describing the Health System Building Blocks that define their core capacities states that “a well-functioning health system ... is built on having trained and motivated health workers, a well-maintained infrastructure, and a reliable supply of medicines and technologies, backed by adequate funding, strong health plans and evidence-based policies”: Guinea, Liberia, and Sierra Leone had none of these. Ten months after the epidemic began, the CDC described the overall state of health services as completely lacking with no personal protective equipment, no training in infection control, and no Ebola surveillance system. In addition, the ties between existing health services and their communities were lacking, with hospitals seen as places to die rather than places to seek care.³⁷ Efforts to stabilize the situation included providing doctors, nurses, medication, supplies, and temporary isolation units. Despite these efforts, case numbers and deaths continued to rise, reflecting the lack of central leadership and the difficulty of adapting to an unknown cultural setting with sustained resistance from terrified communities.

Among all the concerns raised in this desperate situation, one of the most important is the lack of trust between communities and healthcare workers because the classic pattern of epidemic management depends on community engagement for case identification and isolation, contact tracing, quarantine, clinical care, and infection control. This critical component of epidemic response allows information about the outbreak to be absorbed and initiates civilian ownership of the response. Sustained engagement and communication with local community groups builds trust and confidence in response efforts, optimizing necessary social mobilization. When healthcare workers are seen as dangerous aliens – something that can easily occur when groups of white strangers arrive, often in full hazmat gear with face guards and masks – it is easy to see how fear and mistrust can develop. Community members need technically sound and culturally appropriate education so they can participate in case identification and contact tracing, cooperate with quarantine, seek out clinical care, and cooperate with infection control measures. In

an intense disease transmission setting, engagement of individuals, families, and key stakeholders in a community as part of a strong healthcare infrastructure is essential for this to occur.³⁸ During the Ebola epidemic, early efforts at public communication tried to generate behavioral change by emphasizing Ebola's high fatality rates and the absence of a cure. Rather than encouraging the infected to come forward, this messaging drove many suspected cases to avoid testing, and led families to hide their sick members. Community resistance like this was very dangerous because case identification and contact tracing were essential to bringing the outbreak under control. Over time, a focus on reaching out to communities and trying to understand the cultural context of the crisis resulted in community buy-in and ownership of their response. Once established, education about the danger of traditional burial methods and the importance of alternate methods was effectively conveyed along with the need for immediate treatment and isolation of symptomatic individuals, the importance of contact tracing, and the reasons for quarantine of community contacts. For all the sophisticated international efforts that Ebola engendered, it was these community engagement efforts that finally ended the epidemic.³⁹

Even when healthcare infrastructure is excellent, community engagement is important. For example, during the SARS outbreak in Toronto, representatives of Chinese Canadian and other Asian ethnic groups banded together to form the "Community Coalition Concerned about SARS" to provide linguistically appropriate and accurate information about the disease for their community. They established SARS telephone support lines manned by Chinese Canadian volunteers for immediate information access. This was especially important because of the need to explain the reasons for contact tracing and quarantine to interrupt the chain of disease transmission. The group's efforts optimized identification of at-risk individuals and increased the effectiveness of public containment and quarantine policies.⁴⁰

As stated by then WHO Director-General Margaret Chan during the analysis of the Ebola response, "there is no replacement for very strong and good, resilient local health systems with the capability for disease surveillance."⁴¹

The Homefield Advantage: healthcare infrastructure and Community Involvement for Epidemic Preparedness – Progress/Potential

Creating strong national healthcare systems in impoverished countries all over the world is the new gold standard for epidemic preparedness. The post-Ebola position of the WHO addresses this clearly, identifying strong national public health services – a country's existing healthcare infrastructure – as the critical first line of disease defense. The IHR adopted in 2005 require member countries to be prepared for disease outbreaks by certified compliance with a system of mandated "core competencies," the WHO term for the capacity of existing national healthcare systems for surveillance, detection, and control of disease outbreaks.

In the past, the response to a major global pandemic like Ebola involved emergency efforts directed and administered by foreign aid groups aimed almost

exclusively at stopping the spread of disease. Emergency aid workers have been like firefighters arriving at a monstrous forest fire: they are there to put the fire out! Once the fire is out – once the chain of disease transmission has broken – emergency aid groups go home. Their goal has been a rapid response to an emergency situation, not the development of a sustainable healthcare system. As described by Randall Packard in *A History of Global Health*, some of this crisis mentality is a residual of colonial times when groups like the Rockefeller Foundation created International Health Commissions to stamp out diseases like yellow fever in Cuba, Panama, and West Africa. The colonial past of global health often involved providing “disease-focused interventions ... over the development of basic health services.”⁴²

We can see this crisis mentality in many international medical humanitarian responses where global efforts focus on providing specific, emergency interventions like the vaccines provided in the recent yellow fever outbreak in Angola or medications to treat HIV infection in sub-Saharan Africa. By contrast, supporting the development of healthcare systems is a long-term effort coordinated with the population of a country, requiring sustained resources of money and personnel and time. The new plan calls for the WHO to work directly with countries on development of the healthcare infrastructure necessary for surveillance, case detection, patient care, and disease preparedness, as well as coordination of the international response. With these new efforts, the WHO is signaling its recognition of the importance of strong national healthcare systems to prevent lethal, local infectious outbreaks from becoming global pandemics. Whether this massive effort will be successful remains to be seen.

Rebuilding the health systems of resource-poor nations, many of which face critical shortages in healthcare staff and facilities, will require substantial assistance. Access to the necessary financial resources is addressed in the next section. Helping countries to identify critical areas for development and training the necessary healthcare workforce are roles that will also be played by international organizations that more typically have provided temporary assistance during disease emergencies. As described earlier in this chapter, the GHSA, a joint American effort of the CDC, Department of Defense, and the US Agency for International Development (USAID), is partnering with more than 70 countries, international organizations, and non-governmental stakeholders to accelerate the development of strong national healthcare systems by supporting the achievement of the core capacities that certify the competence of healthcare infrastructure.

The CDC’s Frontline Field Epidemiology Training Program is also a good example of using local community engagement to improve epidemic outcomes. FETP-Frontline was launched in 2015 to increase field epidemiology capacity in countries where it was needed most by training staff members from the local Ministry of Health. Community-based disease surveillance strategies can provide real-time disease data at the very outset of an outbreak. A recent analysis of the program identified major improvements in timeliness and accuracy of district-level surveillance reporting, critical factors in an effective surveillance program.⁴³

An adequate, trained, healthcare workforce is a critical component of a strong healthcare infrastructure. However, in 2013, there were 17.4 million fewer healthworkers worldwide than were needed to provide essential primary healthcare services, with the most acute health workforce shortages occurring in Africa and South-East Asia. Many countries already use community healthworkers (CHWs) to effectively deliver health services to the communities in which they live. A substantial body of evidence demonstrates that CHWs increase uptake of health services, reduce health inequalities, provide a high quality of services, and improve overall health outcomes. A current initiative supported by WHO, UNAIDS, and other partners provides technical support to aid national efforts to train 2 million new CHWs across Africa by 2020 – as of this writing in 2019, more than 300,000 new CHWs have been deployed.⁴⁴ The United Nations Commission on a Global Health Risk Framework identified community engagement as a specific high-priority goal and also recommended development of basic disease monitoring at community level using CHWs.⁴⁵ Individual CHWs would be provided with basic surveillance training to allow them to identify unusual health events in their communities and report these to the nearest health center for further investigation using mobile phones.^{46,47} A particular advantage of CHWs is their familiarity to the community and their identification as both community members and as part of the healthcare system. CHWs can function as the first level of a comprehensive national early warning and response systems for new disease events. Training and empowering CHWs will also improve community engagement and education.

A third option for community engagement is involvement of the public in disease detection. Public participation in science dates back thousands of years, but extension into disease detection is relatively recent. Now called citizen scientists, individuals are engaged in a wide array of disease outbreak projects including vector detection and surveillance.⁴⁸ Mosquito Alert is a program that invites citizens to systematically report tiger mosquito sightings using a designated phone app with photo verification. More than 38,400 citizen scientists have been trained and results show that Mosquito Alert facilitated early warning detections in new, previously unidentified regions, and control in areas already colonized. Overall, the results suggest the potential for citizen science to outperform traditional methods for research, surveillance, and control. Mosquito Alert was able to expand across jurisdictions with tiger mosquito identifications far beyond the known invasion front of traditional surveillance methods.⁴⁹

Another example of a citizen-science surveillance approach is the Participatory One Health Disease Detection (PODD) system in Thailand, which applied event-based surveillance models to detect highly pathogenic avian influenza (HPAI) in chicken flocks. Volunteers from 300 villages and 74 community governmental agencies submitted daily surveillance reports of poultry health and disease in their communities using smartphone technology. Real-time analysis of incoming reports allowed rapid detection of outbreaks and the generation of automatic warning messages to activate community contingency plans, including dispatch of a disease investigation team to confirm the outbreak by

clinical examination and laboratory confirmation. During the first 16 months of PDD system piloting, 25 abnormal death outbreaks were detected: eight outbreaks were laboratory-confirmed to be devastating epizootic pathogens. The system demonstrated the potential for early disease outbreak detection at the community level to prevent disease spread.⁵⁰

Participatory disease surveillance supports sharing of health information among community members, enhancing early detection of human and animal diseases while simultaneously empowering communities to take ownership and control of surveillance practices. The widening use of mobile phones in sub-Saharan Africa, where the penetration rate has reached 67%, offers the opportunity to use mobile technology solutions for real-time event reporting. The Southern African Centre for Infectious Disease Surveillance used a participatory surveillance system to enhance early detection, timely reporting, and prompt response to health events in human and animal populations at multiple sites. Community health reporters (CHRs) and facility and district officials were trained to use a mobile phone reporting app. Between 2010 and 2016, the project trained and empowered 82 frontline CHRs and almost 100 support team members in Tanzania, Zambia, Burundi, and Kenya. The health data and associated geographical coordinates collected by CHRs were submitted to a centralized server system that created a spatial distribution of disease events from the latitude and longitude coordinates projected onto the map using the World Geodetic System. Smartphone data from trained citizens has been contributing to improved community engagement and disease surveillance in both human and animal populations in East and Southern African regions since 2010.⁵¹

Supporting the development of strong national healthcare systems for surveillance, detection, treatment, and control of disease outbreaks with an effective infrastructure of laboratories, clinics, and hospitals and an adequate number of trained workers on the ground is a critical goal for infectious disease preparedness. Including community-based systems as part of healthcare infrastructure optimizes engagement, education, and outbreak response. A robust national healthcare system is the true homefield advantage.

IV. Bring Your Checkbook: Current Status

Responding to all the insufficiencies in the global response to major disease crises will require major funding. Inadequate funding at national and international levels was part of the WHO failure to adequately prepare for an overwhelming outbreak emergency like the Ebola outbreak. Historically, public health systems have been part of the governmental structure of individual sovereign states. However, a strong, national public health infrastructure assumes the presence of sustained resources for development and maintenance of appropriate facilities and personnel, trained to manage diagnosis, triage, treatment and infection control. Instead, critical healthcare inadequacies are typical in resource-poor countries like those of West Africa where the Ebola epidemic arose, in sub-Saharan Africa where 70% of people living with

HIV/AIDS worldwide now reside, or north-eastern Brazil where the 2015 Zika epidemic emerged. In analyses of the Ebola epidemic, the absence of even the most basic healthcare system was repeatedly identified as a critical factor in how the outbreak became a rampant epidemic.

Even when an existing public health system recognizes an apparent outbreak, delayed reporting because of concerns about the financial impact on tourism or trade can compromise epidemic management, as it did when SARS first emerged in China. Albeit substantially delayed, the desperate situation in Guinea, Liberia, and Sierra Leone ultimately led to unprecedented international mobilization of health and humanitarian aid – but this kind of crisis-based response is neither sufficient to address basic healthcare inadequacies nor sustainable beyond the short term. Global health security mandates new global approaches to fund infectious disease management. Whereas public health and the appropriate provision of healthcare infrastructure has been considered the sovereign responsibility of countries, the means to fulfill this responsibility are increasingly global, and require international collective action and effective and efficient governance of the global health system.⁵² At the WHO, funding is a critical priority for improved epidemic preparedness and the new director-general will have to establish stable, increased global health funding. In the past, WHO Member States have been reluctant to give the UN organization adequate core funding and much of its income has been tied to specific projects, giving it less flexibility. Going forward, adequate funding for the new WHO agenda and for all the agencies that support global health security is essential.

PEPFAR – the President’s Emergency Plan for AIDS Relief – is an example of the power of national humanitarian aid when appropriately deployed.⁵³ Development of highly effective combinations of antiretroviral medications that suppressed the replication of HIV transformed the lives of HIV-infected people in resource-rich countries beginning in the mid-1990s. However, more than 90% of all HIV infections were occurring in resource-limited countries, particularly in sub-Saharan Africa, where patients had little or no access to ART. In response, President George W. Bush initiated the formation of PEPFAR, an interagency program coordinated by the Department of State, originally providing \$15 billion over 5 years, targeted for prevention of 7 million new HIV infections, treatment of 2 million HIV-infected persons, and care for 10 million HIV-infected people. In May 2003, PEPFAR was launched in 14 countries in Africa and the Caribbean that were severely affected by HIV/AIDS: collectively, these countries accounted for nearly 20 million HIV-infected men, women, and children. Continuously funded with bipartisan support since its inception, PEPFAR-funded programs have treated 13.3 million HIV-infected men, women, and children with ART as of September 2017. Recent PEPFAR data indicate that five African countries are on track to achieve the UNAIDS targets for treatment implementation by 2020. The program has also supported the development of sustainable health system capacity by investing in the critical infrastructure of laboratories and training more

than 220,000 healthcare workers. PEPFAR demonstrates the power of well-funded, targeted support in the global health arena.⁵³ Unfortunately, the Trump administration has systematically cut funds for global relief since 2016 – the 2020 budget proposal from the White House includes \$1.35 billion in cuts to PEPFAR and \$392 million in cuts to the Global Fund to Fight AIDS, Tuberculosis and Malaria compared with enacted fiscal year 2019 levels.⁵⁴

Many private philanthropic organizations play a critical role in funding responses to disease outbreaks independently or as part of private–public partnerships. As an example, the Bill & Melinda Gates Foundation’s Emergency Response Program aims to “reduce suffering, disease, and death in countries affected by natural disasters like epidemics by responding directly to emergencies and investing in strengthening the ability of first responders, their organizations, and local institutions to help communities prepare for and cope with future shocks.” The Foundation has been intensively involved in vaccine development, especially the efforts to eradicate polio and malaria. They also collaborate with other foundation programs to develop and introduce innovative products and approaches that can save lives and build community resilience before an emergency occurs. The emergencies they have responded to have included the Ebola virus outbreak in West Africa, cholera outbreaks in Cameroon, floods and landslides in Kashmir and Nepal, Typhoon Haiyan in the Philippines, and conflict and displacement in the Central African Republic and South Sudan.⁵⁵

Bring Your Checkbook: Progress/Potential

The World Bank’s International Development Association (IDA), established in 1960, provides grants and low- to no-interest loans for projects and programs that boost economic growth, reduce poverty, and improve people’s lives in the world’s 77 poorest countries, 39 of which are in Africa. Two new important World Bank Initiatives were developed in response to the Ebola epidemic.

IDA 18 is a scaled-up commitment to improve pandemic preparedness in at least 25 countries over 3 years through funding of an integrated series of projects supporting development of health care infrastructure and strengthening national, regional, and cross-sectoral capacity for regional disease surveillance and response.⁵⁶ Pandemic Emergency Financing Facility (PEF) is a quick-disbursing financing mechanism that provides a surge of funds to enable a rapid and effective response to a large-scale disease outbreak. Eligible countries can receive timely surge financing if affected by a major disease outbreak with pandemic potential. The PEF is designed to work as insurance for pandemic risk, offering coverage to all low-income countries eligible for financing under IDA.

International organizations and NGOs supporting response efforts in affected countries are also eligible to apply for these emergency funds, which are grant-based and do not need to be repaid. PEF insurance covers large-scale outbreaks of a pre-identified group of diseases including pandemic influenza, SARS and

MERS-CoV, Ebola, Marburg and Crimean Congo hemorrhagic fever, Rift Valley fever, and Lassa fever. The costs of insurance premium payments for the first 3 years have already been committed by donors.⁵⁷

Humanitarian aid is an essential component of global healthcare support, but it is susceptible to change as politics and resources evolve. To date, the PEPFAR program has funded \$70 billion in HIV/AIDS treatment. A program like this is important, not just for its direct funding, but also because it sets an example for how other countries and organizations can effectively address infectious diseases worldwide. Sustaining these levels of support is an important question for the future.⁴⁹

While support from national programs like PEPFAR and private philanthropies like the Bill & Melinda Gates Foundation is important, the focus on a specific health issue can result in programs that function parallel to a country's public health system. Obviously, programs like this can provide good results in achieving specific targets (such as providing antiretroviral treatments to people living with HIV) but work limited to one area can leave the basic healthcare system unchanged when specific issue funding ends. To date, approximately two-thirds of international development assistance for health programming has been allocated to programs addressing specific targets; only a reported 6% has been given to strengthen health systems. Providing a greater proportion of funding to support national implementation of the WHO-IHR Core Capacities would strengthen the infrastructure that underpins a nation's healthcare system. Reluctance to increase budget support due to the perceived weaknesses of governance and financial management systems in less economically developed countries could be addressed by partnering with national health systems to provide both funding and technical support.

One area that will require specific funding is research and development for diagnostic and treatment methods for pathogens which have the potential to initiate a major disease outbreak. In the past, research and development have not often focused on apparently rare diseases that occurred in resource-poor countries. Ebola is an excellent example of this – the virus had caused more than 20 outbreaks since its identification almost 40 years ago but no vaccine had been developed. Guided theoretically by the need to recoup the costs of research and by the opportunity for profit, pharmaceutical companies have focused their efforts on diseases that affect societies whose citizens are willing and able to pay for new products. By contrast, research should be focused on infectious pathogens with the potential for epidemic spread with vaccines, therapeutics and diagnostics developed to the stage where they can be rapidly tested and produced in the event of an outbreak. Dedicated funding is urgently needed to expand this kind of research. Funding mechanisms could include public or private grants, research prizes, advance market commitments, or subsidization of basic research efforts.³³

A fund for emergent research and development in direct response to an outbreak will also be needed.³⁹ The goal of this funding is the immediate characterization

of the epidemiologic, microbiologic, pathophysiologic, and molecular biologic characteristics of the outbreak pathogen, and the development of diagnostic techniques, therapeutic medications and vaccines through Phase I trials so that rapid progression to safe, usable, effective products can be achieved in the face of a disease outbreak.

Robust and sustained investment will be needed to establish an effective system to prevent and respond to disease outbreaks. Ensuring adequate preparedness by supporting the development of appropriate healthcare infrastructure in resource-limited countries, establishing a comprehensive system of early disease detection and response, and targeting research to support these efforts cannot be achieved without substantial financing. However, the investments needed are small compared to the significant costs imposed by epidemics in terms of lives lost and foregone economic growth.

Looking Back :: Moving Forward

The last century has seen a steady increase in the frequency, diversity, and severity of viral disease outbreaks like those we describe in this book. All three of these characteristics have increased even further over the last 40 years. The viruses that caused these outbreaks, most of animal origin, exemplify the variability and rapid mutability that make them so dangerous. In many outbreaks, it is the characteristics of the viral pathogen itself that initiate the outbreak and promulgate the expansion from epidemic to pandemic, in the context of scientific, medical, societal, and environmental change. With unprecedented mobility, increased population density and environmental change, epidemics like HIV/AIDS, SARS, Ebola, and Zika underscore – dramatically and tragically – what we already know: in a world as interconnected as ours, outbreaks anywhere, even in the remotest corners of the planet, have the potential to impact the whole world.

In the past, global panic about an epidemic has often dwindled away before any progress in detection or containment has been made. New issues emerge and push the last disease threat out of the headlines, presaging loss of commitment and funding for health crisis response. While progress sometimes appears to have been made since the last crisis, many countries – especially those that are resource-poor – are still not adequately prepared for a pandemic. Chronic underinvestment in basic public health infrastructure requirements like routine care, disease surveillance, diagnostic laboratories, and emergency operations centers prevents timely identification, response, and containment of a disease outbreak. This is especially short-sighted given the low cost of preparedness relative to the devastating impact of a pandemic. Outbreaks like SARS show that even sophisticated health systems in developed countries can be challenged by the emergence of new pathogens.

There are already many systems designed to respond to global disease outbreaks. All are well intentioned with claims of rapid disease detection and response.

However, analysis of recent epidemics shows most systems are encumbered with administrative complexities that make the response to disease detection ponderous, convoluted, and slow. All the knowledge, all the medical talent, all the available advanced technologies at our disposal are useless if they cannot be activated quickly to respond to the report of a novel disease outbreak. And limitations in basic healthcare infrastructure at the national level in under-resourced countries can significantly compromise all efforts to contain a dangerous, fast-moving viral outbreak.

While the exact source and virulence of the next emerging pathogen are difficult to predict, there is a significant risk that this outbreak could be far more severe than any we have experienced. We know that high population density, increasing proximity between animals and people, climate change, environmental destruction, and increasingly rapid and extensive global travel facilitate viral mutations, spillover from animals to humans and rapid pathogen transmission. Emergence of a virulent strain of a highly transmissible airborne pathogen like influenza could result in millions of deaths all over the world. The impact of a novel virulent virus like this could far outweigh that of the 1918 influenza pandemic, our gold standard for viral pandemic tragedy. Mathematical modeling of pathogen spread has shown that such a disease could spread to all major global capitals within 60 days, and kill more than 33 million people within 250 days. The emergence of such a virulent pathogen is entirely within the realm of possibility.

We can study each new viral pathogen so that knowledge of every aspect of a virus informs our response to diagnosis, therapy, and prevention. We can create faster, smarter response capabilities by strengthening surveillance systems including integration of web-based disease reporting systems. We can expand local disease response by supporting development of effective healthcare infrastructure and maximizing community engagement and front-line disease reporting. We can develop virtual emergency epidemic response teams, ready for mobilization whenever the call comes. And we can create stable ongoing sources of financial support. With conviction and commitment, all these responses are within our reach. Will this be enough?

We must try. Ultimately, the odds that a given virus will cause an outbreak depend on the virus itself, the animals that host it, the people who are at proximate risk for infection, and the environment in which all of us live. Too often, global panic about an epidemic has been followed by complacency and inaction – we cannot let that happen. Development of appropriate healthcare infrastructure and comprehensive disease detection and response capacities, particularly in “hotspot” areas like central Africa and South-East Asia where a confluence of risk factors contribute to disease emergence, is our best option – our only option – for disease containment and interruption of transmission of a new viral pathogen. Because while we are analyzing previous epidemics and developing new strategies and trying to finance the ultimate pandemic response system, viruses are continuing to endlessly evolve into new forms with ever-greater capacity to transmit, parasitize, replicate, and cause new pandemic disease.

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9

AND NOW, AS PROMISED

The 2019 SARS-CoV-2/COVID-19 Pandemic

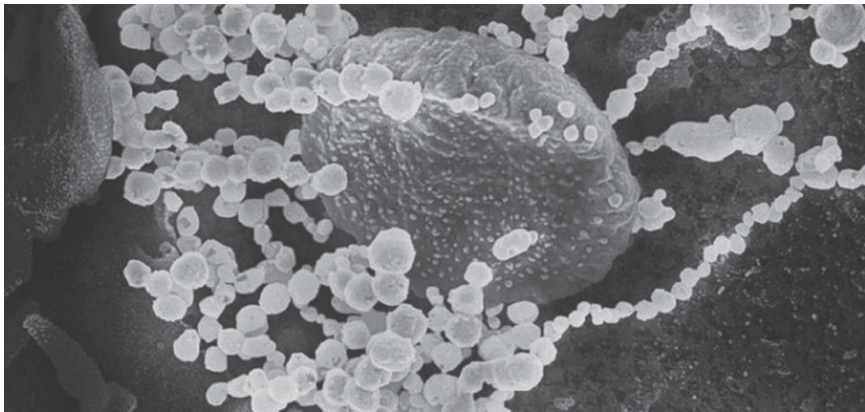


FIGURE 9.1 Novel coronavirus SARS-CoV-2.

Photo credit: National Institute of Allergy and Infectious Disease: NIAID-RML. US.gov

The scanning electron microscope image in Figure 9.1 shows SARS-CoV-2 virions emerging from the surface of cells cultured in the laboratory. SARS-CoV-2, also known as 2019-nCoV, is the virus that causes COVID-19. The virus shown was isolated from a patient in the USA.

#WEWANTFREEDOMOF SPEECH

Unlike all the other chapters in this book, this introductory essay is not a personal story. It is instead the story of a brave young Chinese physician named Li Wenliang, the nature of life in China's repressive and highly censored society, and the power of social media. In late December 2019, Doctor Li, a young ophthalmologist in Wuhan, China noticed that seven patients in his hospital quarantined with pneumonia had cultured positive for a virus resembling SARS-CoV. On December 30, 2019, he messaged his medical school alumni group on WeChat, a popular Chinese messaging app, telling them about the pneumonia patients and suggesting they consider wearing protective equipment at work to prevent infection. In China, memories of the 2003 SARS pandemic are powerful, as are memories of the Chinese government's delay in reporting the original outbreak that allowed global spread of the SARS virus. Li was among the first of a small group of doctors who tried to get the word out about the potential of a new SARS-like outbreak. Within hours, the message had gone viral with Li's name attached.¹

On the same day in December that Li messaged his colleagues, the Wuhan Municipal Health Commission notified the World Health Association (WHO) about the cluster of cases and issued an emergency notice to the city's medical institutions, reporting that a series of patients from Wuhan, many of whom had contact with a local wet market, the Huanan Seafood and Wild Life Market, had a "pneumonia of unknown cause." However, the message also warned that "no organizations or individuals were allowed to release any information to the public without authorization." Stunningly, while the global alarm had been officially raised, local communication measures in Wuhan were forbidden.

Li was called to a local police station on January 3, 2020 and reprimanded for "spreading rumors online" and acting illegally to "severely disrupt the social order" over the message he sent in the chat group. He was forced to sign a formal apology and agree to not discuss the disease further.² Frightened for himself and for his young family, he was grateful to be allowed to return home.¹ But in the days that followed, what had started as a local outbreak exploded, with dramatic daily increases in cases, including cases in healthcare providers, indicating the new disease was spreading directly from person to person. By January 7, a group of Chinese researchers definitively identified the cause of the atypical pneumonia as a coronavirus similar to SARS-CoV. Still, no local measures were taken to provide information or to prevent the spread of infection.

It is dangerous to oppose the government of China. All communication channels are closely monitored and any hint of information that differs from the party line can result in arrest and imprisonment. As an example,

you might remember that the original SARS outbreak began in November 2002 when multiple inhabitants of the Chinese province of Guangdong on the coast of the South China Sea developed a severe pneumonia. It was not until three long months later that the Chinese Ministry of Health notified the WHO that 305 cases of this acute respiratory illness of unknown etiology had occurred between November 16, 2002 and February 9, 2003. Chinese doctors knew this was extreme under-reporting of the number of cases, the severity of the illness and its spread within China and that this misinformation deliberately minimized the importance of the outbreak and, therefore, the global response. Chinese authorities continued to cover up the extent and severity of the disease for months before another whistleblowing doctor, Jiang Yanyong, exposed the crisis through western media, galvanizing the global response that ended the SARS pandemic.² At the time, he was held in military custody for 45 days before international pressure led to his release. More recently Jiang, now 88, has had his contacts with the outside world cut off and movements restricted after he asked the authorities to reassess the 1989 Tiananmen pro-democracy movement. He is now under de-facto house arrest. Yes, it is dangerous to oppose the government of China.³

Li returned to work, but he himself was infected with the new coronavirus when he operated on a patient who did not know she was infected. On January 10, he started to feel sick, and his symptoms progressively worsened over the next 3 weeks. Hospitalized with fever and cough, too short of breath to speak, he decided to fight the government, going public online with details of how he had been silenced in the name of stability. He shared documents online and carried out interviews via text message, including photographs showing him wearing an oxygen mask and holding his ID badge to verify the authenticity of his posts.⁵ His messages allowed reporters to follow the dangerous story of official suppression of the facts at a time when containment of the dangerous new virus was most possible.⁴

Almost overnight, the 34-year-old doctor became a household name in China, identified by millions of people as the voice of truth in the escalating coronavirus crisis. His brave stance, and his illness, were particularly poignant because he is the father of a 4-year-old and his wife is pregnant with their second child. As public anger about the cover-up spread, local authorities did eventually apologize to him and to the seven other physicians investigated for spreading rumors; the central government did finally acknowledge that the crisis had been mishandled in its early days. But the shift to implementation of aggressive local containment measures came too late for the thousands who had already been infected, including Li himself. On a social media post on January 30, he confirmed he was one of thousands of 2019-nCoV-infected patients.

Late on Thursday, February 6, state-controlled media outlets reported that Li had died, triggering an enormous public outpouring of grief. Public assemblies are banned in China, and many overseas Chinese still fear ramifications from attending public events, but messages and flowers were left outside the hospital where he died, and mourning ceremonies and vigils were held all over China and in many sites in North America. On social media, the news was met with a flood of posts expressing grief and anger. An hour after the announcement of Li's death, the trending topic "Wuhan government owes Dr. Li Wenliang an apology" appeared on the social platform Weibo before it was censored. The Chinese ambassador to Washington, Cui Tiankai, said on Twitter, a service the ruling party's internet censorship also blocks the public from seeing, "Really saddened by the death of Dr. Li Wenliang. He was a very devoted doctor. We are so grateful to him for what he has done in our joint efforts fighting against #2019nCoV." In a remarkable act of resistance, millions of Chinese posted: #WeWantFreedomOfSpeech. The government in Beijing responded by censoring every communication.⁵

The massive public response was an indication of how powerfully Li's story had resonated. In death, Dr. Li Wenliang was still the voice of truth, laying bare the facts of the Communist Party's efforts to suppress information about the outbreak and the reality that authorities prioritized maintaining the appearance of control over the health and safety of their people. With his words, Li made recognition of the divide between propaganda and reality, between suppression and truth, inescapable. While state TV broadcasts continued a steady stream of praise for the party's leadership, Chinese journalists with the help of online activists like Li exposed the government's systematic efforts to hide the disease outbreak. In a system designed to crush dissent, he dared to resist, dared to speak truth to power. While critically ill himself, he still exposed the true gravity of the 2019-nCoV outbreak, the incompetence of the government, and the need for aggressive defense. There is no greater hero.

The 2019-nCoV/SARS-CoV-2 Pandemic

On December 1, 2019 when the first reported case appeared in Wuhan, China, it might have seemed inconsequential, just one patient with a community-acquired pneumonia of unknown cause. But Wuhan in Hubei province is a major commerce and transportation hub with a population of more than 11 million people. On an average day, 30,000 people fly out of the city, and many more use bullet trains from three railway stations in the city. Disease spread was inevitable. By December 31, there were 26 more hospitalized cases with the same clinical picture. By January 11, the number had increased to 41 and review of the clinical features of this group revealed a history of fever, cough, and fatigue that accelerated over several days to shortness of breath in predominantly middle-aged men. In all patients, chest

imaging was abnormal with x-ray findings of bilateral patchy pneumonia and/or CT scans showing distal ground glass lobular and subsegmental infiltrates. Within a week, more than half the group had severe breathing difficulty requiring respiratory support and one-third needed ICU care. At the time of the report published on January 24, six patients had died.⁶ Importantly, two-thirds of these patients had worked or shopped at a local fish and wild animal market, the Huanan Seafood Wholesale Market, suggesting a possible origin for the virus. Of major concern is timing: if the first human illness appeared on December 1, infection must have occurred earlier, because of the incubation time – still undefined at that time – between infection and symptoms. If so, the virus could have been spreading silently between people well before the cluster of cases was recognized in late December. Also on January 24, person-to-person transmission of the virus – already strongly suspected because of multiple cases of infection in hospital workers – was definitively confirmed by report of a cluster of five 2019-nCoV cases in a family who had travelled to Wuhan where two family members visited a hospitalized relative.⁷

Against this alarming clinical backdrop, researchers with the China Center for Disease Control investigating the cause of infection in three adults with pneumonia of unknown etiology definitively identified a novel coronavirus from broncho-alveolar lavage specimens just one week later, using whole-genome sequencing, direct polymerase chain reaction (PCR), and culture. Phylogenetic analysis showed that the previously unknown virus fell into the beta-coronavirus genus, which besides SARS-CoV and MERS-CoV, also includes a bat SARS-like coronavirus.^{8,9} Based on the WHO temporary naming system, this new virus was called 2019-nCoV; as of February 11, 2020, it is SARS-CoV-2. The Huanan Market was closed on December 31 and the China Center for Disease Control reported on January 26 that of 585 collected samples, 33 tested positive for the virus. The 33 samples came from 22 stalls and a garbage vehicle in the market, most in the area where wild animals were traded. Further public results of this investigation are still pending.¹⁰

A focus on these dates in January is important because of the Chinese New Year festival, which begins with the first new moon of the lunar calendar and ends on the first full moon, 15 days later; in 2020, the first day fell on January 25 and the festival lasted until February 8. This is the most important holiday of the year in China and involves travel for millions of people reuniting with their families. Travel by rail is the preferred mode of transportation with almost all Chinese people on holiday, and trains are densely packed with tightly confined families. I can think of no better environment for viral transmission.

On December 31, the Wuhan Municipal Health Commission announced the outbreak and alerted the WHO, but in the two weeks that followed, the Wuhan health authorities remained the only official source in China for updates on the outbreak, reporting no new information despite the identification of the pathogen as a new coronavirus very similar to SARS-CoV by Chinese scientists on January 7. An expert team from the Chinese Ministry of Health visited Wuhan in early January, reporting that there was no person-to-person transmission and that the

outbreak was well controlled after the closing of the Huanan market. For a week, no new confirmed cases were announced and local health authorities maintained there was “no obvious evidence for human to human transmission,” and “no infection of healthcare workers” despite multiple reports to the contrary by medical professionals on social media; the outbreak was represented as “preventable and controllable.”¹ At this critical turning point, the Chinese authorities put secrecy and order ahead of openly confronting the growing crisis and risking public alarm or political embarrassment – publicly portraying the outbreak as a well-managed situation, completely under control. As one small example, when the Huanan Market was closed for culturing and disinfection, the state-run news agency reported that it was being closed for renovations.

For the next two weeks, local health officials continued to assure the public that there were no new cases in Wuhan and no cases at all outside the city. This inaccurate portrayal of the outbreak allowed the virus to spread widely in Wuhan, to other cities in China, and to the world. It was not until definite person-to-person transmission was confirmed with 2019-nCoV cases reported outside of China in Thailand and Japan, as well as in Chinese patients who had had no exposure to the Huanan market that the Minister of Health sent a second expert group to Wuhan on January 19. This time, person-to-person transmission was immediately confirmed – including multiple cases in local doctors and nurses – and a national response was finally triggered on January 20.

Then came what was reported as a sudden jump in infections. Until January 17, only 41 cases of the virus had been reported. By January 20, that number had soared to 198. After the central government took over management on January 20, President Xi Jinping ordered “resolute efforts to curb the spread” of the coronavirus and explicitly stressed the need for the timely release of information – this was the first time Xi had publicly acknowledged the outbreak. Later that evening, a government-appointed respiratory expert, known for fighting SARS 17 years ago, declared on state-broadcasted CCTV that the new coronavirus was transmissible from person to person. Three days later, on January 23, authorities abruptly placed a complete lockdown on Wuhan, eliminating all forms of transportation and effectively sealing off the city. Other cities across Hubei Province rapidly instituted their own travel restrictions, putting much of the province of 59 million people in a de-facto lockdown. But by then, an estimated five million people had already left the city for the Lunar New Year holiday. And by January 24, when the information on the original 41 patients was published worldwide with the Wuhan lockdown in place, the number of confirmed 2019-nCoV infections in Wuhan had increased dramatically to 835 with 25 deaths, a much faster progression than at any time in the SARS outbreak.¹¹ Early suppression of critical knowledge about the outbreak squandered a critical window of opportunity when an informed Wuhan populace could have potentially changed its behavior to limit the virus’ spread.

During the next two weeks, the epidemic grew exponentially with the number of cases doubling approximately every seven and a half days. The epidemic spread

rapidly throughout and beyond China, exacerbated by Lunar New Year travel. By January 25, confirmed cases in mainland China stood at 2016, but there were already seven cases in Thailand, six in Hong Kong, five in Macau, five in Australia, four in Malaysia, four in Singapore, three each in France, Japan, South Korea, Taiwan, and the United States, two in Vietnam, one in Nepal, and one in Sweden; all cases outside of China were linked to travel to the Wuhan area or contact with travelers who had returned from Wuhan. While the Communist Party struggled to control spread of the virus throughout China, the majority of adjoining countries including Mongolia, Nepal, North Korea, Russia, Tajikistan, and Vietnam ordered immediate, partial closure of their borders with China and many international airlines reduced or suspended service to China.

The Virus

With this growth in cases, scientists in China and around the world attempted to characterize the state of knowledge of the virus and the disease at that critical moment in time. Identification of the causative virus as a coronavirus provided important basic information very early in the epidemic (Figure 9.1).^{8,9} As a group, coronaviruses (CoV) are large, enveloped, positive-strand RNA viruses divided into four genera: alpha, beta, delta, and gamma; alpha and beta CoVs are known to infect humans. Four CoVs are endemic globally and cause 10–30% of mild upper respiratory tract infections in adults. However, two new well-known beta-CoVs – SARS-CoV and Middle East Respiratory Syndrome CoV (MERS-CoV) – have already caused epidemics of severe respiratory illness with high mortality just in the last 20 years. Coronaviruses are ecologically diverse with the greatest variety seen in bats, the suggested reservoir for these viruses.

The 2019-nCoV virus – now officially known as SARS-CoV-2 – is physically large among viruses, measuring 125 nm in diameter, covered with spiky projections – the surface spike glycoprotein is critical for binding to host cell receptors and is believed to represent a key determinant of host range restriction (Figure 9.2). Genetic analysis of samples from nine newly diagnosed patients in Hunan showed 99.98% sequence identity, indicating a very recent emergence of the virus in humans. 2019-nCoV/SARS-CoV-2 is genetically distinct from SARS and MERS, although the spike protein of the new virus is similar to the SARS surface spike. When the 2019-nCoV sequence is compared to a library of viruses, the most closely related are two SARS-like bat viruses, leading to the theory that this novel virus is also of bat origin with a currently unknown animal species potentially acting as an intermediate host between bats and humans.

We know that the original SARS-CoV infects lung cells using angiotensin converting enzyme 2 as a receptor; with the noted phylogenetic similarities between 2019-nCoV/SARS-CoV-2 and the original SARS-CoV on whole-genome sequencing studies, it is postulated that the novel coronavirus may also use the same host cell receptor. An important CoV factor is their ability to expand their genetic diversity through ongoing recombination and mutation events. As

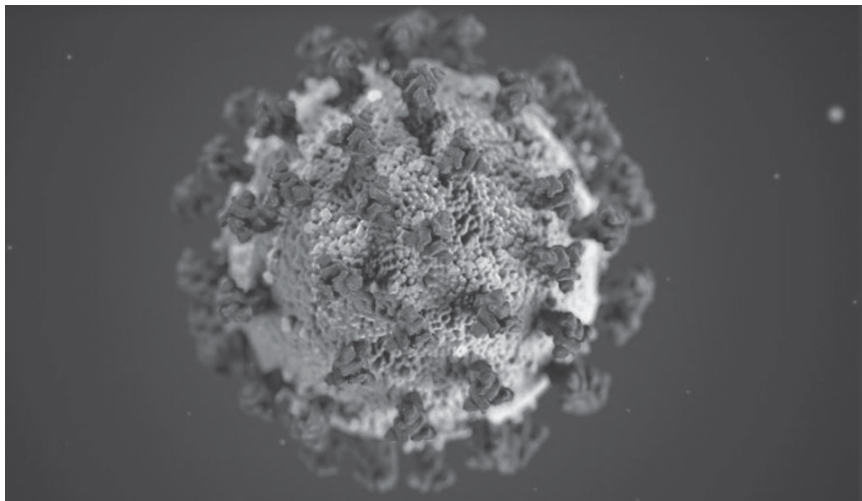


FIGURE 9.2 Computer rendering of the coronavirus 2019-nCoV/SARS-CoV-2.

with SARS, many scientists suspect that an unknown animal infected by bats with 2019-nCoV spread the virus to humans at the live seafood and wild animal market in Wuhan where many of the early cases were documented. With SARS, the intermediate host is thought to have been a palm civet. With 2019-CoV/SARS-CoV-2, the chief suspect is the pangolin, a small ant-eating creature and the world's only scaled mammal; pangolins are prized in Asia as food and medicine. Pangolins were being sold in the now infamous seafood and wild animal market in Wuhan, linked to early cases of 2019-nCoV/COVID-19. The genome sequence of the novel coronavirus strain derived from pangolins was 99% identical to that from infected people, China's official Xinhua news agency reported, suggesting that pangolins could potentially be the intermediate host between bats and humans.¹²

The Disease

Crucial findings with any new disease include the range of clinical severity, the extent of transmission and rates of infection – all remained unknown at this stage despite more than 71,000 cases of COVID-19 and 1600 deaths, as of February 17, 2020. The virus spreads both directly – through physical transfer between people through close contact with oral or nasal secretions – and indirectly, through contact with droplets deposited on nearby surfaces when an infected person coughs or sneezes, which can then be carried to the eyes, nose or mouth of a healthy subject. We do know that 2019-nCoV/ SARS-CoV-2 is too big to stay suspended in the air for any significant length of time or to travel more than a few feet and this should limit transmission. As with SARS, droplets generated during medical procedures can be aerosolized, augmenting the potential for infection of healthcare providers. Hand hygiene for both infected and uninfected individuals and personal

protective barriers – gowns, gloves, masks, and goggles – reduce droplet transmission. Estimates of the basic reproduction number or R_0 for the virus – the number of additional persons one case infects over the course of their illness – have generally ranged from 2.2 to 3.6, but there are estimates as high as 6.5.¹³ (An R_0 of less than 1 indicates very low transmission potential; the higher the R_0 , the greater the potential for sustained transmission. As an example, the R_0 for measles is 18!)

According to the WHO, most coronavirus cases reported to date have described a mild illness; in clinical series, 82% have been mild, 15% severe and 3% critical.¹⁴ Published details from three series of laboratory-confirmed, hospitalized cases in Wuhan, China give us preliminary epidemiologic characteristics and transmission dynamics.^{15–17} The median age of patients was 55–59 years with no cases in children below 15 years of age; in all of these early series, the majority were male. Patients with earlier onset of symptoms were slightly younger, more likely to be male, and much more likely to report exposure to the Huanan Seafood Wholesale Market. In later cases, a majority of patients had no exposure to the market, supporting the increasingly important role of human-to-human transmission. The proportion of cases acquired in hospital by patients or hospital personnel increased over time, to 40% in one series. Based on exposure history and onset of symptoms, the mean incubation period was 5.2 days, with the 95th percentile of the distribution at 12.5 days. This preliminary estimate supports a 14-day medical observation/quarantine period for exposed persons. The most common clinical symptoms were fever, present in 80% of patients, followed by cough in 70%, shortness of breath in 30%, and muscle ache in 10%. Upper airway symptoms were notably absent. Bilateral pneumonia was present in 75% of these hospitalized patients on chest x-ray and/or CT scan with multiple areas of consolidation and ground-glass opacifications. The median time from first symptom to hospital admission was 7 days; ~60% of this hospitalized group developed acute respiratory distress syndrome at a median of 8 days after the first symptom. Mortality ranged from 4% to 17%, predominantly in older patients, with deaths due to progressive respiratory and multi-organ failure. Overall, mortality was estimated at ~2%.

Major questions remained: What was the course in non-hospitalized but sick patients and in patients with mild symptoms? What proportion of patients have no symptoms at all? (Remember that with polio, 95% of infected individuals have no identifiable symptoms at all but they are still contagious and infectious.) What was the location and duration of viral replication and shedding in patients with varying degrees of illness severity? (Again, with polio, remember that the virus is shed in stools and infectivity can last for weeks after any signs of illness have resolved.) How long is viral survival on surfaces? What is the susceptibility, severity, and infectivity in children? What is the true infection rate of the virus? (With Zika, sero-surveys showed 66% of the population of French Polynesia had evidence of infection with the virus, but only 30% had been diagnosed.) Finally, what are virus-specific humoral and cellular immune responses in mild, moderate, and severe cases of COVID-19? Does transmission take place before the onset of symptoms as suggested by a single case report? When are infected people most contagious? Right after they contract

the virus? Only after symptoms begin? Or, do they become increasingly contagious over time? How long does the contagious stage last? The answers to these questions are critically important for development of the most effective epidemic response.

Diagnosis

Identification and genetic analysis of 2019-nCoV allowed early development of three diagnostic techniques: isolation of the virus itself; positive RT-PCR assays; or identification of a genetic sequence that matches 2019-nCoV.^{8,9} In practice, RT-PCR assays have been the method of choice. Beginning in January, the WHO published laboratory guidance for detection of the novel coronavirus including advice on biosafety, patient sampling, and pathogen detection and characterization. Within days of obtaining the sequence data, PCR assays were developed for clinical diagnostic use by multiple academic and public-sector groups, including the China Center for Disease Control. These publicly available assays target areas of the genome for detection of sequences specific for 2019-nCoV/SARS-CoV-2.

Globally, the WHO has established a network of specialized referral laboratories with expertise in the molecular detection of coronaviruses to serve as support for national laboratories performing diagnostic tests in their own countries. WHO is also working to ensure global test availability, sending 250,000 coronavirus tests to more than 70 laboratories around the world, as well as 500,000 masks, 350,000 pairs of gloves, 40,000 respirators, and nearly 18,000 isolation gowns to 24 countries. Early in the outbreak, there were only two laboratories in Africa – one in Senegal and one in South Africa – which could test samples. The WHO goal is for 29 countries in Africa to have established diagnostic testing capacity.

China is making major efforts to address rapid diagnosis. A commercial nucleic acid reagent test kits and a sequencing system for the virus have been developed which can reportedly generate test results in 30 minutes. The complete kit is expected to speed up the diagnostic process and expand the supply capacity of virus detection products.¹⁸

Reports of diagnostic capacity in China vary widely. A statement from the Wuhan Municipal Health Commission said a total of 10 biosafety laboratories could test nearly 2000 samples every day when at full capacity. It was not clear when these laboratories would be fully functional. The city reportedly planned to transport 30,000 diagnostic kits to the laboratories, but by February 10, only 6000 had been issued. According to another municipal health authority, there are 31 institutes certified for nucleic acid tests, capable of testing 4000 virus samples every day. A new laboratory for 2019-nCoV testing opened on February 5, within seven days of construction. The laboratory, named Fire Eye, is reportedly capable of handling 10,000 samples a day, with the “latest facilities and technology for safe and highly efficient viral nucleic acid testing.”¹⁹

By contrast with this organized plan, the situation on the ground in China appears chaotic with reports of long lines of masked citizens awaiting testing. From multiple online sources, test kits and laboratories are in short supply. According to a

post on the Chinese micro-blogging site Weibo, “only those with severe symptoms can be tested due to shortage of kits in Wuhan, with a wait time of 5–6 hours for testing. In the surrounding area in Hubei province ... only a small batch of test kits was delivered, only enough to treat less than one-tenth of the number of people waiting to be checked at the hospital.”²⁰ As described further in the section on response to the outbreak, there were major delays in diagnostic screening because of test kit/laboratory shortages and the overwhelming volume of individuals seeking care.

In the United States, the CDC also developed a laboratory test kit – the Real-Time Reverse Transcriptase (RT)-PCR Diagnostic Panel for 2019-nCoV/SARS-CoV-2 testing. The test was intended for upper and lower respiratory specimens from individuals who meet criteria for COVID-19 and had been FDA-approved for emergency use. However, within days of its release to pre-selected laboratories across the country, performance problems were identified and the test kits were recalled. At the time and going forward, the CDC guidelines allowed SARS-CoV-2 testing *only* in individuals who had been potentially exposed to the virus by travel to Wuhan, China or close contact with recent Chinese travelers. Testing could only be done with the CDC test kit and the test samples had to be sent to the CDC with a turnaround time of 48 hours. This situation remained in place until February 28, 2020.

CDC scientists have successfully grown 2019-nCoV/SARS-CoV-2 in cell culture, using a clinical specimen from the first US patient infected with the virus. The isolate is available from a central repository at the National Institutes of Health to microbiology, medical and infectious disease researchers.²¹ The CDC has also been uploading the entire genome of the viruses from reported cases in the United States to GenBank as sequencing is completed.

Treatment

There is as yet no specific treatment for 2019-nCoV/SARS-CoV-2 infection. Supportive care is being maximized, including the use of lung bypass with heart–lung machines to rest the lungs and allow recovery when mechanical ventilation is no longer effective. In case series, doctors have been trying a variety of antiviral medications like the anti-influenza drug, oseltamivir (Tamiflu) as well as standard antibiotics when a patient’s clinical condition deteriorates.^{15–17}

At this stage, there were reportedly 34 interventional studies in China that were recruiting subjects, designed to investigate multiple aspects of care including antiviral medications, use of steroids/glucocorticoids and selected ventilation techniques. As one example, a randomized, controlled trial to investigate the safety and efficacy of the investigational antiviral compound remdesivir is underway with the collaboration of the developer, Gilead Sciences, and the US Food and Drug Administration, the CDC, China’s Center for Disease Control and Prevention, and the World Health Organization. Remdesivir is a nucleotide analogue prodrug initially developed as a treatment for Ebola and Marburg virus infections. In animal models, the drug has

shown activity against other coronaviruses like SARS. A Phase I study has already demonstrated the safety, tolerability, and pharmacokinetics of remdesivir in healthy volunteers. China started a randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of remdesivir in hospitalized adult patients with mild and moderate 2019-nCoV infections on February 3, 2020. It will enroll 270 patients in the China–Japan Friendship Hospital in Beijing and is expected to be completed by the end of April.²²

As of February 25, 2020, a parallel randomized, controlled trial of remdesivir will begin at the National Quarantine Unit at the University of Nebraska. Thirteen people repatriated by the US State Department from the *Diamond Princess* cruise ship were transported to the Quarantine Unit, on the UNMC/Nebraska Medicine campus in Omaha on February 17, 2020. The passengers were in a close setting where there had been significant spread of COVID-19 and were sent to the unit for continued isolation and possibly further care. The CDC has since reported that 11 people in the UNMC unit have confirmed SARS-CoV-2 infection and they will hopefully participate in the trial.

Prevention/Vaccine Development

On January 23, the Coalition for Epidemic Preparedness Innovations (CEPI) announced that it will give three companies a total of \$12.5 million to develop 2019-nCoV/SARS-CoV-2 vaccines. CEPI is a nonprofit organization formed in 2016 solely to support development of new vaccines against emerging infectious diseases. Already available for potential evaluation in humans are three candidate vaccines for SARS-CoV and five for MERS-CoV. In response to CEPI's announcement, three different research proposals have emerged.²³

The Vaccine Research Center at the US National Institute of Allergy and Infectious Diseases is working with the vaccine-maker Moderna. Based on the gene sequence of the virus reported by Chinese researchers, the company will utilize a messenger RNA platform previously shown to trigger an immune response in animals. Using this methodology, Moderna has already developed a vaccine for MERS-CoV, but this had only been tested in animals. Incredibly, Moderna created a trial SARS-CoV-2 vaccine just 42 days after the genetic sequence of the virus was described. The first batch has already been shipped to NIAID with Phase I human testing planned as early as April 2020.

Inovio is another company working on a 2019-nCoV vaccine with help from CEPI. Inovio produces DNA-based vaccines and its MERS-CoV vaccine has already entered human trials. That vaccine relies on the spike protein, a focus for the potential new 2019-nCoV/SARS-CoV-2 vaccine. Inovio says they could have enough vaccine produced within one month to begin animal testing.

CEPI's third grant is going to Australian researchers at the University of Queensland who are developing a vaccine consisting of viral proteins produced in cell cultures. Their goal is to have a candidate vaccine ready for human tests in 16 weeks.

Once candidate vaccines are available, researchers will test them in animals before launching Phase I human trials, testing safety and immune responses in small numbers of volunteers. In parallel to the human trials, researchers will test the vaccine's ability to protect an animal model intentionally exposed to the virus. Successful vaccines will then be tested in large human trials. This process generally takes up to 18 months but it can be accelerated: if you recall, Ebola vaccine trials were initiated at the end of the 2014–2016 epidemic in West Africa with rapid validation of an effective vaccine used very effectively in two subsequent Ebola outbreaks in the DRC.

Xinhua, China's state news agency, reported that a mouse trial of a candidate mRNA vaccine against 2019-nCoV launched on February 9, 2020. Testing is said to be at a very early stage; the next step will be toxicity tests in larger animals. No further details are available.²⁴

Epidemic Response: China

China has been on the front line of a full-fledged war with 2019-nCoV/SARS-CoV-2. According to the WHO, China has less than two physicians for every 10,000 residents, so response to this overwhelming epidemic has been frenetic and desperate. By report, Hubei healthcare workers have been exhausted and overwhelmed with testing kits and personal protection equipment, such as face masks, hazmat suits, goggles, and gloves, all in short supply. Hospitals and care providers without adequate protective gear have been struggling with staff shortages, unable to respond to everyone seeking care.²⁵ In Wuhan, patients have faced hours-long lines to receive medical care, the BBC reported.²⁶

There are ongoing reports that people with symptoms of the virus have been denied admission to local hospitals in Wuhan because of limited beds and the requirement that all admissions must have tested positive for the virus. Footage from a Wuhan hospital shows doctors attempting to treat patients in incredibly crowded conditions. Videos from *The New York Times* and social media show throngs of people packed into narrow hospital corridors, awaiting diagnostic testing.²⁷ Incredibly, China built two new 1000-bed hospitals in just two weeks to help relieve the severe shortage of hospital beds and improve care for the many newly infected people. But even with these, hospitals are overwhelmed, and more huge new shelters are being erected to warehouse patients. All medical resources remain in short supply. According to a Rand report, "many hospitals in China are overwhelmed by the large volume of people with symptoms coming for testing and treatment because of the fear of the epidemic. Patients are often being turned away and delayed diagnosis and uncounched deaths are both possible."²⁸

As days passed and patient numbers continued to increase, more sites in Hubei province enacted wartime measures, sealing off residential complexes and allowing only essential vehicles on the roads. Chinese authorities took the unprecedented step of announcing plans to suspend all outbound transportation from Wuhan in a further effort to contain the illness. Ongoing confusion remained, caused by

increasingly restrictive public calls for action at the top and a chaotic situation on the ground.

Epidemic Response: International

Led by the WHO, the international community swung into action beginning in the third week of January when they convened an advisory Emergency Committee to review the situation in China. By their second meeting on January 30, person-to-person transmission had been confirmed and there were increasing numbers of cases in China and in other countries; the Committee concluded the outbreak had become a Public Health Emergency of International Concern (PHEIC) and that same day, Director-General Tedros issued a declaration to that effect. Following a January 28 meeting in Beijing between China's President Xi Jinping and the WHO Director-General, China accepted the involvement of an international WHO-led collaborating team to work with Chinese counterparts on outbreak control. On February 5, WHO announced a \$675 million 2019-nCoV/SARS-CoV-2 preparedness plan to provide international coordination and operational support, optimize readiness and response capacity, and accelerate research and innovation. The WHO organized a "Global Research and Innovation Forum" to mobilize international action in response to the 2019-nCoV emergency on February 11–12 in Geneva. At the outset of the meeting on February 11, the WHO Director-General announced that the illness caused by 2019-nCoV now had an official name: COVID-19: the CO stands for corona, the VI for virus and the D for disease. In addition, the International Committee on Taxonomy of Viruses proposed a name for the novel coronavirus that causes COVID-19: the new name is SARS-CoV-2, which, according to the naming committee, "formally recognizes this virus as a sister to severe acute respiratory syndrome coronaviruses."²⁹

Around the globe, individual nations have developed their own responses to the epidemic. For example, in the United States, President Trump announced the formation of the President's Coronavirus Task Force on January 29, led by the Department of Health and Human Services and coordinated by the National Security Council. As of January 30, 2019-nCoV/SARS-CoV-2 was declared a public health emergency in the United States. The Department of Homeland Security issued instructions for quarantining US citizens and permanent residents returning to the United States after stays in China and barring the entry of other foreigners with recent travel to China. The Department issued a Level 3 advisory for travel to China. The Department of Homeland Security's Customs and Border Protection and the CDC have announced enhanced health screenings for travelers from Wuhan, China, at three points of entry to detect travelers who are potentially ill: New York, San Francisco, and Los Angeles.³⁰ The State Department has evacuated non-emergency US personnel and their family members and private US citizens from Wuhan beginning with the evacuation of 195 American state department employees and their families on January 29, with the group quarantined for 14 days. On February 5, two more planes carrying about 350 Americans out of

Wuhan arrived at military bases in California and arrivees were placed in 14-day quarantine.

Original responses by other countries had generally been less aggressive but nearly all developed plans for dealing with the virus. The majority of adjoining countries including Mongolia, Nepal, North Korea, Russia, Tajikistan, and Vietnam ordered partial closure of their borders with China. Hong Kong officials closed more than half the border crossing points to the mainland and shut down all high-speed rail and ferry services to China. In India, passengers coming from China were to be scanned at the airport and those who show signs or symptoms of the virus quarantined. More than 20 countries including the United States, Canada, Singapore, Philippines, Uzbekistan, Saudi Arabia, Indonesia, and Thailand have evacuated their own citizens. Notable exceptions to this are Pakistan, Cambodia, and most African nations. British prime minister Boris Johnson called an emergency cabinet meeting to discuss the outbreak and country preparedness and on February 7, the UK Chief Medical Officer raised the risk to the public from low to moderate based on increasing person-to-person transmission. The Foreign and Commonwealth Office advised UK nationals to leave China where possible. On January 29, Russian president Vladimir Putin held a meeting on measures to counter the spread of coronavirus in Russia. Since February 2, pool journalists around Putin have been required to have their body temperature checked for signs of illness. On February 17, Russia temporarily suspended entry of Chinese citizens due to the coronavirus outbreak, banning them from traveling to Russia for employment, tourism, or education. Taiwan banned all international cruise ships from docking and most international airlines reduced or suspended service to China. American and Delta airlines announced they would begin canceling flights from the United States to China. International carriers, including British Airways, Air France, Lion Air and Lufthansa group also announced they are canceling flights to China.

Mid-February Assessment

This epidemic has evolved very rapidly. By February 14, the total number of cases in mainland China had surged past 70,000 with more than 1500 fatalities officially reported by the Chinese National Health Commission from mainland China. Cases were reported across all provinces in China, with 81% in Hubei Province; 68% of these cases were from Wuhan City, the epicenter of the outbreak. China's National Health Commission said more than 1700 medical workers had been infected with coronavirus, six of whom had died.³¹

There had been consecutive explosive daily increases in new cases, ranging from 31% to 91% from mid-January until January 28, after which the rate slowed to 19–28% with a suggestion of a plateau.³² On February 10 and 11, *no* new cases were reported: had quarantine efforts in China actually been successful? Then, on February 12, *14,850 new cases* were reported, the largest single-day increase since the outbreak began.

The explanation lay in a change in how Chinese officials were diagnosing 2019-nCoV/SARS-CoV-2 infection. Without notice, on February 6, the Chinese National Health Commission announced that asymptomatic individuals who tested positive for the virus but did not show clinical symptoms would no longer be counted as confirmed cases. This reduced the total number of positives reported and explains the decline in cases over the preceding days; it also meant that potentially contagious individuals had been excluded from official reports.

Then on February 12, the Hubei government abruptly adopted a new, broader definition for confirmed cases, now including clinically diagnosed patients – patients diagnosed by their symptoms plus CT scan evidence of pneumonia – but without PCR testing. Apparently overwhelmed by masses of people with symptoms and no available, rapid testing, Chinese authorities changed the way they diagnosed COVID-19, using the combination of clinical symptoms and positive lung scans which produces immediate results, rather than the longer process of PCR testing. This new methodology accounted for the dramatic increase in daily confirmed cases on February 12.³²

Changing the way cases were diagnosed at this stage of an epidemic made it impossible to accurately estimate the true scale of the epidemic and undermined efforts to determine the resources needed for response. However, diagnosing 2019-nCoV/SARS-CoV-2 infection with the combination of symptoms and positive lung scans would get patients into needed care more quickly. A dramatic change like this reflected the desperate situation on the ground with scores of sick and undiagnosed individuals waiting for care. Eliminating people who are test-positive and symptom-negative meant that a significant number of infected people will not have been counted in the official tally of the outbreak. While comparing case numbers from week to week had become meaningless, it seemed obvious at that time that there had been no plateau in new COVID-19 infections.

There was enormous, ongoing concern about global extension. British researchers had published a theoretical study predicting the spread of the virus over the next 3 months. The researchers used international flight itineraries and mobile phone location data to plot the paths of almost 60,000 Wuhan residents who fled during the critical 2 weeks before the outbreak city was locked down. Their analysis estimated that 59,912 air passengers including 834 infected with 2019-nCoV flew from Wuhan to 382 cities outside of mainland China before January 23. The top 10 global destinations for Wuhan travelers were Thailand, Japan, Hong Kong, Taiwan, South Korea, the United States, Malaysia, Singapore, Vietnam, and Australia, but there were multiple sites in Africa.³³

February 14 turned out to be the peak of reported new cases in China and the beginning of a steady increase in cases reported from other countries, which had begun with confirmed cases in Japan, Thailand, and South Korea as early as January 20. By far the largest numbers of cases were in Asia. Outside China, 573 cases had been diagnosed in 26 other countries as of February 14 with three fatalities. There were 15 cases in the United States and nine in the United Kingdom, the latter all linked to the same individual, a British man who contracted the virus at a business

conference meeting in Singapore from January 20 to 22. More than 100 people took part in the conference, including at least one Chinese national from Hubei province – 12 cases of COVID-19 had been linked to this meeting. The British national travelled to a ski resort in the Alps with a group of British friends who all stayed in the same chalet from January 24 to 28. He developed fever after his return to England and was diagnosed with COVID-19. Five other people who had contact with him at the French ski chalet were then confirmed to be infected. The index British citizen has been called a “super-spreader,” a term coined during the SARS epidemic to describe someone who infects a disproportionately large number of people with a virus. The exact definition of a super-spreader varies from one outbreak to another, but this case demonstrates very dramatically the potential for sustained person-to-person spread of SARS-CoV-2. On February 13, the WHO media briefing reported particular concern about instances of onward transmission, like the one in the United Kingdom. The WHO was also very concerned about spread of the virus to Africa, where the first case of COVID-19 had just been reported in Egypt.³⁴

Another special cluster of COVID-19 cases outside of China was on the *Diamond Princess* cruise ship which had been quarantined in Yokohama, Japan since arrival on February 3. The ship carried 3700 passengers and crew and was to be quarantined in the harbor for at least 14 days after a passenger who had been on the ship late in January tested positive for coronavirus in Hong Kong. As of February 18, 542 passengers – a number which had been increasing every day – had tested positive for the virus, the largest cluster of COVID-19 cases outside of China. Concerned about exponential increases in new cases, the United States evacuated asymptomatic American passengers from the ship on February 16, to be quarantined for an additional 2 weeks in the United States. US officials confirm that among the hundreds of Americans evacuated from the *Diamond Princess* ship, 14 tested positive for SARS-CoV-2 and had to be isolated on board the flight home. Adding these patients to those already diagnosed meant there were 29 known culture-positive individuals in the United States at that time.³⁵

Emerging Epidemiologic, Virologic, and Clinicopathologic Picture

A major epidemiologic review of more than 70,000 cases hospitalized with COVID-19 in China provided important clinical and epidemiologic information.³⁶ While 87% of cases were 30–79 years of age with 3% over 80 years, only 2% were less than 20 years of age. There was a minor male preponderance. Symptoms of fever and mild respiratory symptoms developed an average of 5–6 days after infection with a range from 1 to 14 days. The spectrum of disease severity confirmed earlier reports with mild disease in 81%, severe disease requiring at least some respiratory support in 14%, and critical disease requiring intensive care in 5%. The median time from symptom onset to clinical recovery for mild cases was approximately 2 weeks compared with 3–6 weeks for patients with severe or critical disease. Overall, the

case fatality rate was 2.3%, but it increased dramatically with age, to 8% in patients aged 70–79 years and 14.8% in patients over 80 years. Among those with clinically critical disease, the mortality rate was 49%.³⁶

Information on viral dynamics in infected patients is emerging from serial findings in SARS-CoV-2-infected individuals. Viral loads in throat swab and sputum samples peaked at ~5–6 days after infection; this pattern is distinct from SARS, where viral load typically peaked at around 10 days after infection. Sputum samples generally showed higher viral loads than throat swab samples. Viral load was highest early after symptom onset, but in a single patient who died, viral load was persistently very high. Stool samples from a small subset of patients were weakly positive.³⁷

A major series of more than 1000 patients correlated chest CT scan and RT-PCR results.³⁸ On initial evaluation, 59% of patients had positive RT-PCR results and 88% had positive chest CT scans. In patients with positive RT-PCR results, the sensitivity of chest CT in suggesting COVID-19 was 97%. In patients with negative RT-PCR results, 75% had positive chest CT findings suggestive of COVID-19 infection. Initial CT findings were consistent with COVID-19 prior or parallel to the initial positive RT-PCR results in 60–93% of cases. These findings suggest that chest CT may be considered as a primary tool for diagnosis of COVID-19 infection in epidemic areas, especially when RT-PCR results may be delayed.³⁸

Early results suggest the virus is not being transmitted as widely or as easily as seasonal flu or the common cold. In a study, of more than 320,000 blood samples from community members, investigators in China found that less than 1% were positive for COVID-19 antibodies. Information about transmission from asymptomatic people remains limited but small series of individuals who were under active surveillance because of a history of exposure to SARS-CoV-2-infected patients showed positive results on RT-PCR a day before symptom onset, confirming what would prove to be a critical characteristic, that asymptomatic individuals can be infectious.

The time of SARS-CoV-2 survival and the conditions affecting viability in the environment are still currently unknown. According to studies assessing the environmental stability of other coronaviruses, MERS-CoV and SARS-CoV can persist on inanimate surfaces like metal, glass, or plastic for up to 9 days but can be efficiently inactivated by surface disinfection with alcohol, hydrogen peroxide or bleach solutions within 1 minute. There are no data on the transmissibility of coronaviruses from contaminated surfaces to hands.³⁹

February 14 to February 28, 2020

As it happened, February 14 proved to be an early tipping point in this epidemic. After that date, the number of new cases in China steadily decreased while the number in sites all over the world – 50 different countries as of February 28 – gradually but steadily increased. By February 28, there had been a total of 84,124 cases

with 2862 deaths – almost 79,000 of those were in China and 2700 deaths had occurred in Hubei. But on that day, China reported 327 new cases while South Korea with a total of 2337 cases – the largest number outside of China – reported 511 new cases. Half of these were related to an outbreak that started in a church, reflecting the ongoing importance of person-to-person spread in close quarters. There were new and increasing numbers of cases outside of China, as shown in Figure 9.3. There were cases in northern Italy, in Iran and in Japan, as well as in three different countries in Africa. In response to this escalating situation, the WHO raised their Outbreak Risk Assessment Level to “Very High,” the level just below designation as a global pandemic.⁴⁰

Follow-up of the *Diamond Princess* cruise ship is revealing. Originally passengers were “quarantined” on board, confined primarily to their cabins. With each passing day, new cases of COVID-19 were identified, suggesting that the ship was actually serving as an incubator for the virus. During February 16–17, the US government assisted in the repatriation of 329 US citizens or residents from the ship on two chartered flights. As of February 23, 36 (11%) of these repatriated persons had tested positive for SARS-CoV-2 and were receiving medical care. Quarantine with repeated testing was ongoing for the remaining passengers. To that time, this group were the largest proportion of SARS-CoV-2(+) patients in the United States. As of February 28, more than 700 *Diamond Princess* travelers had tested positive for the virus and six had died.

While case numbers had been increasing all over the world, the number in the United States had been very stable. An explanation for this emerged on February 26 when a woman from California with no history of travel or contact with any potentially infected people was reported to be in serious condition with COVID-19. In reporting her case, it was revealed that the CDC had denied testing for SARS-CoV-2 for 5 days after her presentation, despite a diagnosis of pneumonia of unknown etiology, because the patient did not meet the defined travel/exposure criteria for testing.⁴¹ In other words, testing was not being performed for the very clinical symptoms that defined the original outbreak! As of February 23, the CDC had tested only 479 persons from 43 states for COVID-19, almost all related to the original travel/exposure requirements. By comparison, South Korea had already tested more than 78,000 people.

In response to news coverage of this situation, the CDC released expanded criteria for testing on February 27, 2020 to include patients with a “severe acute lower respiratory illness (e.g., pneumonia, ARDS) requiring hospitalization and without an alternative explanatory diagnosis” and “no identified source of exposure.”⁴² That announcement came as the CDC rushed to distribute new SARS-CoV-2 testing kits to state and local health departments amid concerns the virus had already spread beyond individuals known to have recently traveled to a country affected by outbreaks. Initial rollout of test kits had been compromised by problems with the original tests, but on February 29, the FDA announced an “accelerated policy ... to achieve more rapid testing capacity in the United States,” allowing academic hospital laboratories capable of performing high-quality testing to develop and

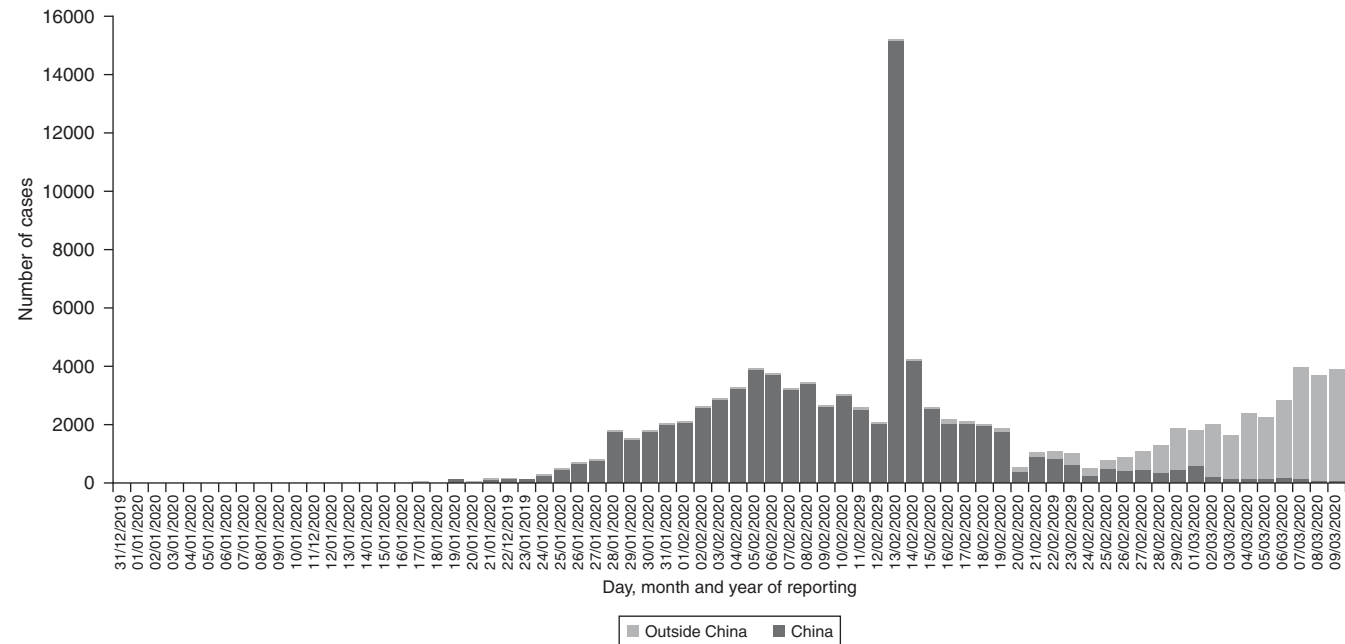


FIGURE 9.3 Distribution of laboratory-confirmed cases of COVID-19 worldwide, December 12, 2019–February 25, 2020.

Source: Wikimedia Commons.

begin using their own tests to detect COVID-19.⁴³ Previously, hospital laboratories weren't sent test kits by the CDC and the FDA required an extensive review process even if the hospitals had internally validated their own tests. Under the new policy, the FDA review would still be required, but laboratories would be able to start using their diagnostics once they were internally validated.

As of March 1, 88 cases of coronavirus had been identified in the United States. The first case was announced on January 21, but the new testing criteria saw a marked uptick in the pace of diagnoses: 22 US cases were announced in just 2 days on February 29 and March 1, including the country's first two deaths, both in Washington State. Washington state had the United States' first confirmed case of coronavirus, announced by the Centers for Disease Control and Prevention on January 21 in a man who had returned from Wuhan, China. This individual had been living in the community for at least several days before he developed symptoms during which he could have spread the virus locally. This week, based on genetic sequence analysis, the virus in another case that was diagnosed on February 28 was found to very likely be descended from the virus in that first case. The two people live in the same county but are not known to one another, and the second case occurred well after the first was no longer contagious. These genetic findings suggest that the virus has been spreading through the community for close to 6 weeks.⁴⁴

Looking Back :: Moving Forward

There are three essential requirements for a global pandemic to occur: emergence of a new agent that infects humans; little or no population immunity to that agent; and easy pathogen transmission from one person to another: SARS-CoV-2 has them all. The speed of transmissibility and the strength of infectivity exemplify the power of this newly emerged pathogen. Still, it is hard to believe the rapidity with which this epidemic has evolved – the first rumors about a new coronavirus outbreak emerged just 9 weeks ago. The current numbers are staggering, but because the outbreak is evolving in real time, we can't yet see the total picture of those infected. This means calculation of things like the fatality rate is impossible – although we probably have a reasonable handle on the number of people who have died, we still do not know the number with mild or no symptoms who no one knows are infected. An enormous hidden population like this sounds alarming, but a multitude of survivors who had minimal or no symptoms means a multitude of individuals with immunity, and herd immunity like this could theoretically mean a dwindling population of susceptible people and even, ultimately, the end of the outbreak.

Unfortunately, even if case identification was perfect, experts warned that as asymptomatic or very mild cases occurred and strict isolation efforts decreased, a new wave of cases would develop in international sites where only isolated cases primarily linked to contact with China were originally present. In China, the vast majority of reported cases have had moderate to severe symptoms; by

contrast, confirmed infections in other countries have come largely from evacuees and have had milder symptomatology. Based on a combination of these statistics, epidemiologists estimated that only one in 19 people infected with the virus was being tested and that the true number of infected people was more than 800,000 as of February 11.⁴⁵ And experts were definitely right about disease spread. Less than 5 days ago, isolated cases were reported in 29 countries; as of February 28, there are reported cases in 50 countries with spiraling numbers in multiple locations including South Korea, Japan, Italy and Iran.

In the United States, the absence of testing did not mean absence of disease – in only the 3 days since the CDC liberalized testing criteria and with still only a limited number of test sites, the first community-acquired cases were confirmed. On February 29, Washington state reported the first death in the US from the new coronavirus, the first healthcare worker to be infected with the disease, and most worrying, the first known outbreak in a long-term care facility. Community transmission has clearly been established and US cases are on the rise.⁴⁶

China's stringent quarantine efforts did limit disease spread as confirmed by the WHO, but even with this massive effort in a compliant population, there were 84,124 cases with 2862 deaths in just 9 weeks and reports of new cases continue with the potential to increase again as citizens return to work and normal social interactions recur. The possibility of effective large-scale public health interventions on this scale in other countries – especially the United States – is low. As predicted, with ongoing exportation of pre-symptomatic cases, local spread is occurring with self-perpetuating outbreaks developing all over the world.⁴⁷ To this point, the WHO has resisted calling this a pandemic – but this is just a question of time and semantics. It is still possible that some combination of quarantine and travel bans and viral decrease in response to increasing herd immunity and rising temperatures will first halt the outbreak and then kill off the virus, and the world will never see 2019-nCoV/SARS-CoV-2 again. After all, that's what happened with SARS in 2003. At this moment with the epidemic evolving all around us, it seems much more likely that we will experience a true global pandemic, an expanding outbreak whose ultimate scope and duration is unknown. We are at a critical tipping point with the progressive increase in involved countries and independent self-sustaining person-to-person spread established in multiple sites around the globe, including many major population and transportation centers. To this time, the majority of cases have occurred in the Northern Hemisphere in sites with well-developed health infrastructure – reports of cases in Africa and South America suggest a much more difficult situation for public health interventions in the future.

While the final trajectory of the 2019-nCoV/SARS-CoV-2 outbreak is impossible to predict, it is clear that a successful response anywhere in the world will require prompt action, from enforcement of classic public health strategies to development and implementation of effective countermeasures. It might still be possible to limit further spread of infection by even more stringently reinforced measures that limit population mobility and close person-to-person contact outside

the home. Isolating cases, quarantining contacts and social distancing have been poorly tolerated in China and, I suspect, tolerance will be even lower in other settings, but they are critical measures to limit disease spread. One area that can be improved based on the experience in China is open and transparent communication at every stage – an informed public that understands the risks and the rationale for proposed interventions is much more likely to cooperate. Many Chinese people, including health experts, have said that the epidemic illustrated the risks to public health created by official censorship, which early in the epidemic led to doctors being silenced by the authorities after they discussed the outbreak with colleagues. As this chapter's opening essay described, one of those doctors, Li Wenliang, died from the virus, making him a martyr-like symbol of the costs of speaking out. Regrettably, Mr. Xi has given no indication that loosening censorship is on his agenda. On March 1, he said the government would continue to crack down on “concocting and spreading rumors” – the accusation that the police in Wuhan leveled against Dr. Li.⁴⁸

The current outbreak of SARS-CoV-2 is yet another example of the importance of infections at the animal–human interface, and the concerns that arise from the emergence of a newly identified organism as it spreads through human populations and across national and international borders. Yet another epidemic of human disease caused by a virus that lives in bats underscores the perpetual challenge of emerging infectious diseases and the importance of ongoing, sustained global preparedness. Although it feels like a barn-door exercise, China's decision to eliminate the zoonotic source of viruses like these by banning wild game markets in China will potentially be important to prevention of future zoonotic events.

There is hope. In this rapidly evolving international health crisis, the COVID-19 outbreak has already transformed how scientists communicate with a flood of information released and dissected on social platforms and in the media every day. Medical journals have created “coronavirus information hubs” and are getting manuscripts reviewed, edited, and published at record speed. Using the GISAID platform established as an international site for scientific sharing of influenza genomic information, SARS-CoV-2 viral genomes are posted and analyzed by evolutionary biologists who can share information from phylogenetic analyses directly. Research addressing critical needs is already underway. Vaccine platforms are in development, including an ongoing clinical trial in humans. Remembering the success of an effort like this during the Ebola epidemic suggests that a vaccine may soon be available to address the progressive wave of global infections. Treatment trials are in progress and with such high patient volumes, these will show results in the relatively near future. An important research focus is the development of consistent, rapid-response, point-of-care PCR testing in low-risk settings – images of packed hallways and waiting rooms where Wuhan residents waited for testing have already inspired the development of novel testing methods outside of usual point-of-care settings, including reports of drive-by testing. As this potential global tragedy continues to unfold, our whole planet needs to be prepared with plans for population education, communication, movement management, and

personal protection. This includes securing adequate supplies of personal protective equipment, drugs, diagnostic tests, supplies, hospital beds, and healthcare personnel, all critical shortages that could develop anywhere in an explosive global pandemic.

This is a people's war and we are all in this together. We must be ready.

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EPILOGUE

June 16, 2020

As it turned out, we were not ready. News reports and just-released scientific papers had allowed me to track the SARS-CoV-2 story as it emerged from a cluster of atypical pneumonia cases in one Chinese city to the brink of a true global pandemic. But somehow, it still felt like there was time. I knew this was an impending disaster – that we needed to leap to battle stations, to activate all systems – but the danger still felt remote, like a distant, still-evolving storm.

That complacency ended in early March, 2020 when COVID-19 exploded in multiple sites all over the world. In Italy, a cluster of cases in the northern Lombardy region became a major outbreak with 1,000 confirmed cases by March 1 despite local quarantine imposed a week earlier. Case numbers and deaths rose dramatically and a nationwide shutdown was imposed on March 4. In a foreshadowing of outbreaks all over the world, emergency and hospital services were completely overwhelmed, with shortages of personal protective equipment (PPE), hospital beds, ventilators, and personnel. Military trucks were needed to transport bodies to crematoriums in nearby towns. Literally tons of medical equipment and teams of physicians from all over Europe and Asia arrived to help with the catastrophic situation. The outbreak peaked with more than 6,000 new cases and 760 deaths on April 1, followed by a slow decline with a gradual easing of restrictions. As of June 15, there have been 237,290 cases and 34,371 deaths in Italy due to COVID-19.

The pattern of the Italian outbreak proved prophetic in countries all over Europe with a similar sudden and explosive rise in cases, particularly in Spain and Great Britain. In response to a severe lockdown, new cases peaked in Spain on March 16 at 8,271 and the death toll surpassed that of mainland China on March 25. Great Britain delayed any effort to isolate citizens with therefore no true peak and decline in cases, instead experiencing an ongoing outbreak with almost 300,000 cases and 42,000 deaths by June 15. On March 11, the WHO declared COVID-19 to be a global pandemic and by March 13, when the number of new cases exceeded those in all of China, Europe was declared the epicenter of the pandemic with cases by

country doubling every two to four days. By March 31, more than one-third of humanity was under some form of lockdown.

Meanwhile, in the United States, an early effort by the administration – a February 2 travel ban to prevent entry of foreign nationals with recent travel to China – was followed by a month of inaction with almost no testing and consistent downplaying of any threat by President Trump. On March 4, confirmed case numbers suddenly jumped from only a handful to more than 100. Only one week later, there were almost 1,300 cases and 50 deaths. Trump announced new restrictions on foreign travelers from 26 European countries and declared a state of national emergency on March 13. Led by state governors, shelter-in-place efforts were urgently introduced and by April 7 roughly 95% of all Americans were under some form of lockdown. Despite these efforts, case numbers and deaths continued to increase. By April 25, the US had more than 905,000 confirmed coronavirus cases and 52,000 deaths, a mortality rate of 5.7% percent. With more cases and deaths than any other country in the world, the US was the new epicenter of the pandemic.

A significant proportion of US COVID-19 cases occurred in New York City (NYC), where early infections were acquired not from Chinese contacts but from European travelers. Case numbers grew exponentially: on March 20, with 5,683 confirmed cases in NYC, the governor issued statewide shelter-in-place restrictions but by March 25 – only 5 days later – over 17,800 cases had been confirmed. Major efforts to expand health care facilities included creation of a field hospital in Central Park and use of US Navy ships offshore in NY harbor. Severe shortages of PPE occurred here as they had all over the world. The city's infection rate was five times higher than the rest of the country with one-third of total confirmed US cases. Explosive growth in cases and deaths continued until April 12 when both categories began to gradually but steadily decrease, followed by a progressive withdrawal of shelter-in-place restrictions. By June 15, the US total confirmed case number was 2.1 million with 116,000 deaths, the highest national total in the world; there had been 215,000 cases and 21,000 deaths in NYC alone.

A tragic feature of the COVID-19 pandemic emerged in the US: the critical involvement of nursing homes. At least 10,000 US deaths took place at senior care facilities – an estimated 27% of all deaths nationwide. In at least six states, nursing home fatalities accounted for half of all COVID-19 deaths. Ultimately, investigation by the WHO revealed half of all coronavirus fatalities in Europe could similarly be traced to nursing homes.

THE VIRUS AND THE DISEASE

Early reports from China proved accurate in describing the basics of SARS-CoV-2 and the characteristics of COVID-19 but, with time, emerging research illustrated the extremely efficient droplet spread of this virus. Reports of global superspreading events demonstrated significantly increased infectious risk associated with prolonged periods in crowded, indoor spaces. The importance of infection by asymptomatic or pre-symptomatic individuals was confirmed: the CDC estimated this pattern of

spread to be responsible for ~35% of infections. These combined findings eventually led to the US recommendations that the general public maintain a physical distance of 6 feet, wear masks and limit the size of social gatherings – all efforts to limit person-to-person droplet spread.

Original reports from Wuhan accurately described a progressive respiratory illness. Subsequent studies during global spread revealed the important involvement of vascular injury and hypercoagulation. Global outbreaks confirmed the dramatic increase in disease severity and mortality with increasing age. In China, the major disease co-morbidities aside from increasing age were related to pulmonary problems; by contrast, the most common comorbidities in subsequent sites were hypertension, obesity and diabetes. New modelling results from international data estimate that the average fatality rate ranges from 0.05% in Iceland to 1.3% in northern Italy. In individuals over 65, the fatality rate in the worst-case scenario is estimated to be ~3.2%. Many methodological issues complicate these calculations but the lower estimates are encouraging. Nonetheless, by June 15, at least 8 million cases of COVID-19 have been confirmed worldwide, with 435,000 deaths.

New treatment options have emerged from active research protocols underway since the earliest days of the pandemic. A randomized trial of intravenous remdesivir in hospitalized adults showed those who received it had significantly shorter recovery times than those who received placebo. Mortality rates were also lower but those results did not quite reach statistical significance. A triple combination of three anti-viral agents – interferon beta-1b, lopinavir–ritonavir, and ribavirin – in patients with mild-moderate COVID-19 disease showed a significantly shorter median time to negative cultures for study patients. Avifavir is a direct antiviral agent that disrupts coronavirus reproduction. The drug has been used in Japan since 2014 against severe forms of influenza and preliminary trials in COVID-19 patients have shown that it shortens recovery time. In response to evidence of abnormal clotting, systemic anticoagulation (AC) has shown impressive results: in-hospital mortality in ventilated patients who were anti-coagulated was 29% versus 63% for those who did not receive AC. Most recently, low-dose steroid treatment with dexamethasone reduced deaths by one-third in ventilated patients and by one-fifth in patients requiring only oxygen. Results like these suggest that in the relative short term, a combination of agents will be defined to effectively address all COVID-19 presentations.

There has been impressive progress in vaccine development. Optimistic experts hope that a viable vaccine against SARS-CoV-2 may even be ready by the end of 2020, with more than 150 potential vaccines under study. For two candidate vaccines, phase II testing in humans has already begun and the beginning of large scale, phase III testing of one of these based on messenger RNA technology is set for next month. Scientists at Oxford University have developed a vaccine from a weakened adenovirus combined with genes of the SARS-CoV-2 spike protein which triggers production of antibodies against the virus. A phase I/II clinical trial began in April in the UK to assess safety and efficacy in healthy volunteers and recruiting has begun for phase II/III trials.

The final trajectory of the SARS-CoV-2 pandemic is impossible to predict. Despite signs of progress, the pandemic roars on with rising caseloads in multiple US states and dramatic increases in case numbers and deaths in South America and Africa. Meanwhile, the pandemic has lost impetus in the eyes of many, as masses of citizens throughout the US and around the globe gather daily in the streets to express outrage over the public execution by suffocation of the African American George Floyd by a white police officer, and the urgent need for social justice reform. This is an especially hard day for any useful reflection for me: I return from a “White Coats for Black Lives” march with the refrain of “Black Lives Matter” ringing in my ears to news that Dr. Li Wenliang’s son was born yesterday. That poignant reminder of Li’s efforts to bridge the divide between propaganda and truth is even more remarkable in light of the highly politicized response to the pandemic in the US and other countries since his tragic death. Of all the knowledge that has emerged so far, perhaps recognition of the need for integration between science and policy, and the accurate communication of that information to the public is the most important revelation of all.

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